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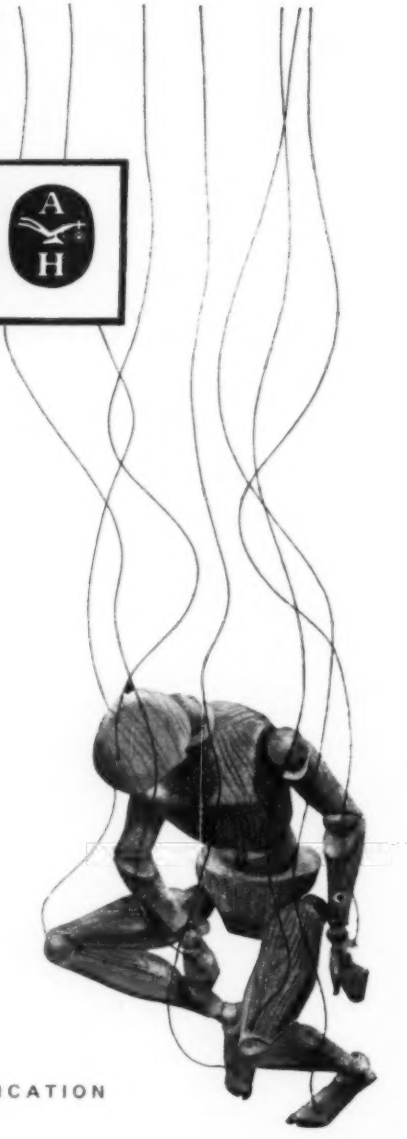

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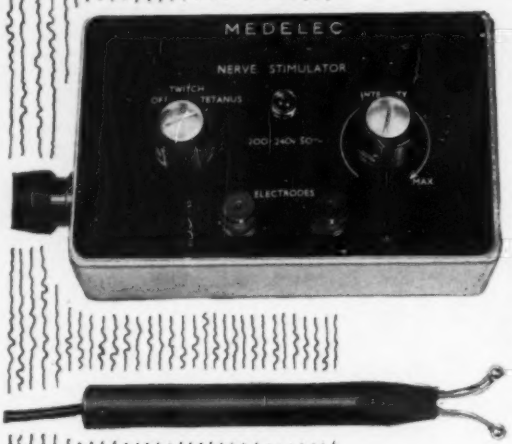

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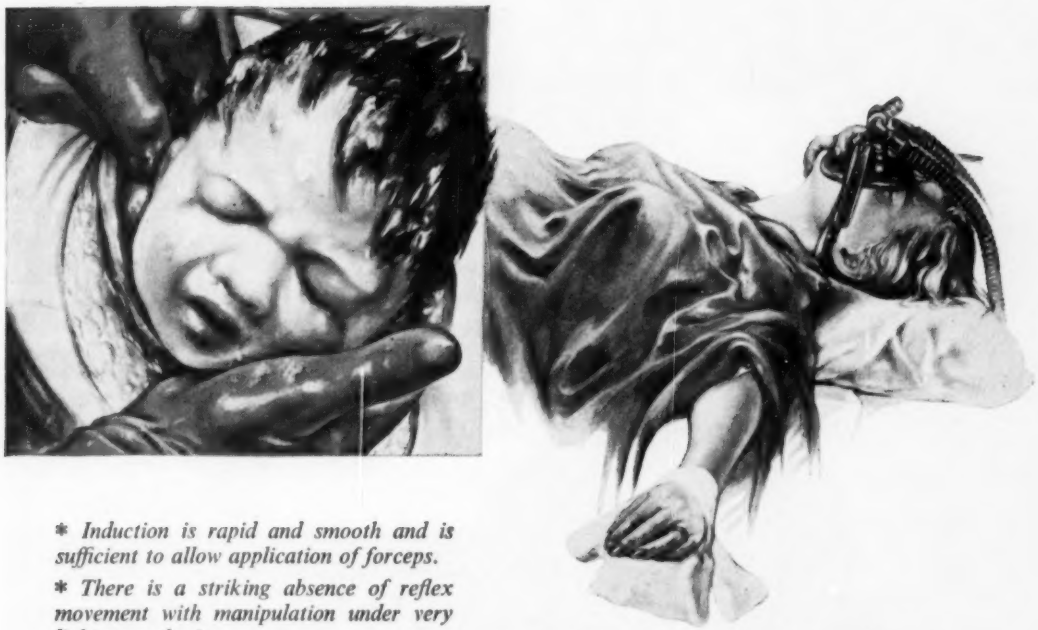

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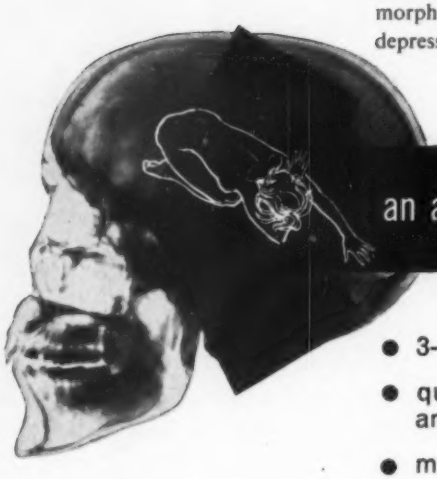

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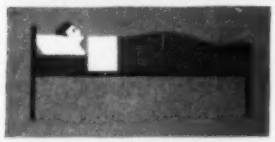

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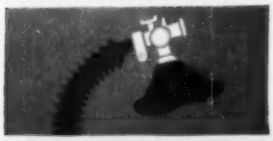

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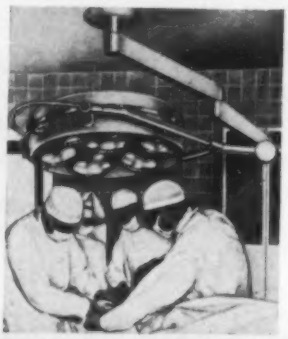

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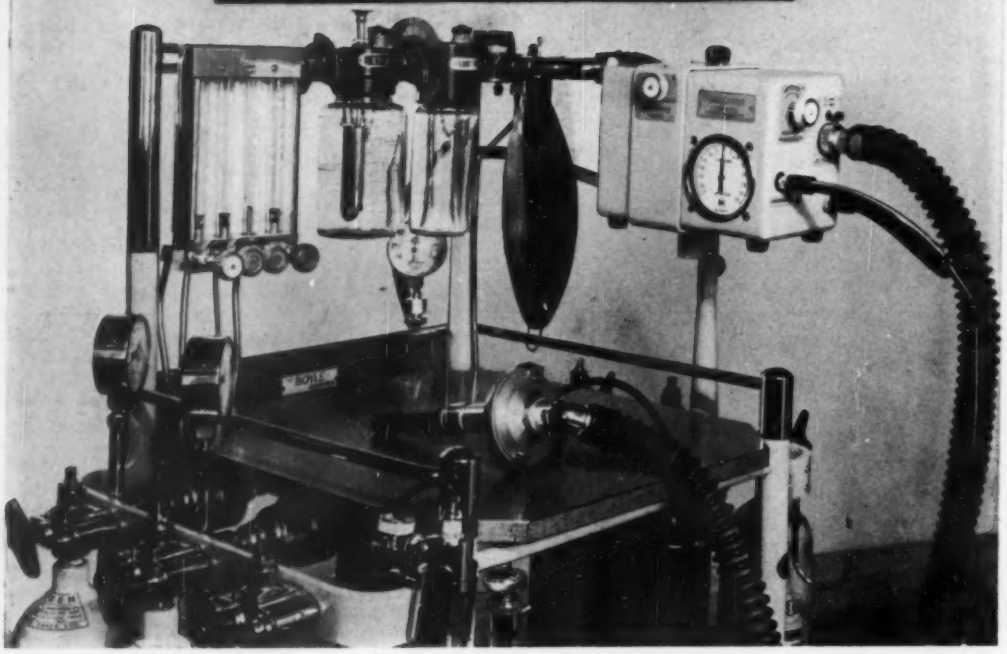

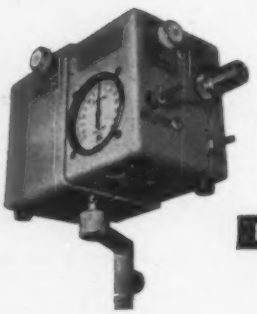

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BRITISH JOURNAL OF ANAESTHESIA

VOL. XXXIII, No. 2 FEBRUARY 1961

EDITORIAL

THE TORONTO CONGRESS

We are very pleased to be able to publish in this issue six of the number of interesting papers presented at the meeting of the World Federation of Societies of Anaesthesiology held at Toronto, last September. To those who had the opportunity of attending the meeting the outstanding memory will be of all the friendly contacts made with colleagues from every part of the globe and these were facilitated by the excellent social programme organized by the local committee. Indeed, it is probably true to say that the very obvious popularity of this type of gathering stems, to a great extent, from the joy and considerable benefit to be obtained from informal discussion and exchange of views.

Nevertheless, to many anaesthetists such a forum of worldwide opinion is an irresistible stimulus to the public announcement of their latest discoveries and conclusions. There is no doubt that fatigue steals over the "congressionists" and the average brain becomes numbed by the bombardment of the mass of information, illustrations and debate. In any case, there were always two or three theatres of activity and it was impossible for an individual to attend even all those papers in which he was interested. For these reasons many will regret the absence of a published proceedings of the Congress, although a summary of all the papers presented was available through the good offices of Geigy Pharmaceuticals.

The papers we are able to publish will only go a small way to remedying this situation. It is hoped that readers will find much of interest.

Brit. J. Anaesth. (1961), **33**, 62

OBSERVATIONS ON THE CEREBRAL EFFECTS OF PASSIVE HYPERVENTILATION*

BY

JOHN S. ROBINSON AND T. CECIL GRAY

Department of Anaesthesia, University of Liverpool, England

By 1952 there had developed a strong clinical impression that the use of controlled respiration for abdominal surgery carried out under thiopentone, relaxant, nitrous oxide anaesthesia, resulted in a reduction in the dosage of both relaxant and barbiturate. This led to the suggestion by Gray and Rees (1952) that controlled respiration, quite apart from its use to achieve adequate ventilation, supplemented in some way the anaesthetic and relaxant drugs being used. Dundee (1952) in controlled observations on patients undergoing upper abdominal operations of 2 hours duration confirmed that there was a reduction in dosage of thiopentone necessary but found less evidence of the need for a smaller dosage of relaxants. He associated these results with the lowered blood acidity which he found almost invariably accompanied controlled respiration. This work has been supported by Gray and Geddes (1959) who drew attention to the appearance of slow wave activity in the e.e.g. during nitrous oxide, oxygen relaxant, controlled respiration anaesthesia and produced some evidence that this was attributable to hyperventilation. They also pointed out that the work of Bonvallet and Dell (1956) suggested that the blood tension of carbon dioxide had an important influence on the activity of the reticular area of the mid-brain, and they suggested that depression of the reticular activating system under conditions of respiratory alkalosis might account both for the appearance of slow waves and for the increased potency of nitrous oxide which was clinically evident.

Ever since Kety and Schmidt (1946) showed that hyperventilation reduced cerebral blood flow, many workers have believed that the cerebral effects of hyperventilation are due to hypoxia. Indeed, Clutton-Brock (1957), who demonstrated a rise in pain threshold in actively hyperventilating subjects, made observations which appeared to support this hypothesis. As hyperventilation is common during the "controlled" respiration of modern anaesthesia, it seemed important to investigate further the cerebral effects of hyperventilation and if possible shed light on their aetiology.

METHOD

The twenty medical students and research workers on whom these experiments were performed were fit males with an age range of 21 to 43 years; only two subjects exceeded 30 years of age.

Passive hyperventilation was produced with a Technicon Huxley pump and thoraco-abdominal cuirass (fig. 1). When the pump was set to apply to the cuirass positive and subatmospheric pressures of $\pm$ 40 cm of H_2O at a rate of 24/min, this respirator proved capable of ventilating conscious subjects with very high minute volumes. It was realized that these conditions of hyperventilation only approximated to those present in the hyperventilation of anaesthesia, but other methods were not practicable with conscious volunteers.

The ventilation achieved was measured as the expiratory minute volume using the anemometer described by Wright (1955). Using the method of Brooks and Wynn (1959), arterialized venous blood was drawn into heparinized syringes, the deadspace of which had been filled with neutral oil. The pH of this blood was measured anaerobically at 38°C in a micro-flow glass electrode system (E.I.L.) by means of a potentiometer (E.I.L. model 33C) and an electrometer having a high sensitivity and stability (E.I.L. model 33B). The P_{CO_2} was estimated using the anaerobically separated plasma by a modification of Astrup's (1956) interpolation method (Robinson and Pimblett, 1961).

*Paper read at the second meeting of the World Federation of Societies of Anaesthesiology, held in Toronto, Canada, in September 1960.

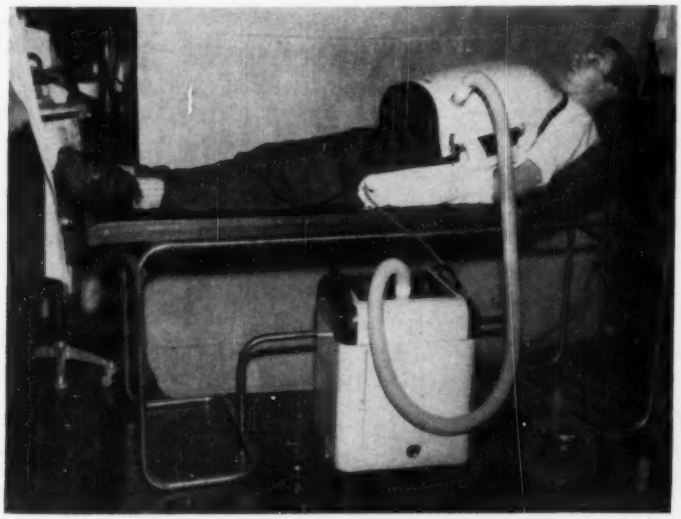

FIG. 1

Cuirass and respirator used to produce passive hyperventilation. The electrical heating pad used to obtain arterialization of venous blood can be seen.

Observations.

During the course of the experiments the following observations were made:

Pain threshold. The pain threshold was measured by the application of a spring-loaded plunger rod to the tibia. The pressure necessary to cause the subject to show evidence of pain was recorded in kilogrammes on a sliding scale affixed to the plunger.* Using this method, two distinct responses to the stimulus were obtained.

The subject was asked to raise his hand when the pressure became painful. This was designated the "pain threshold".

When the pressure was continued evidence of unbearable pain was shown by facial wincing or withdrawing of the leg. This was designated the "pain response". Dundee and Moore (1960) working independently described an almost identical method and reported on its accuracy.

The initial "threshold" response fell with constant repetitive distraction such as the ticking of a metronome or the regular rhythm and noise of the respirator. The second "response" reading was found to be unaltered by distraction and therefore this alone was used during the course of the experiments.

Towards the end of the experiments when, as will be shown later, a plateau of rise in pain threshold had been established, the effects were observed of the inhalation of the following:

Concentrated ammonia vapour.
0.18 ml of amyl nitrite.
A very high flow of oxygen through an open circuit for 4 minutes.

Fundal vessels. Direct retinoscopy during hyperventilation showed constriction of the retinal vessels. It was considered that changes in the retinal vessels might well mirror those in the vessels of the brain and therefore fundal examination was carried out from time to time during the experiments.

Cerebral function. Other changes in cerebral function were difficult to estimate. However, some assessment of mental agility could be made by exercises in simple mental arithmetic and by conversation. During the experiments, there were signs of changes in the mental attitude of the

* This apparatus is manufactured by Messrs. Baird and Tatlock Ltd.

subject and the help of a psychiatrist was enlisted to elucidate these effects.

RESULTS

Pulmonary ventilation achieved.

The pulmonary ventilation achieved varied greatly from subject to subject and from period to period. Most of these subjects achieved values for pulmonary ventilation of 30 l./min or more; two reached the remarkably high figure of 50 l./min. The values and changes in pulmonary ventilation produced in these subjects are discussed elsewhere in greater detail by Robinson (1960). However, in no case in this series was the ventilation value lower than 17 l./min.

pH and Pco_2 values.

At the end of 1 hour this method of hyperventilation in these subjects gave a mean pH value of 7.69 $\pm$ 0.17. Values for pH as high as 7.88 and 7.76 were recorded in two subjects, but in one subject, who had a barrel-shaped and rigid thoracic cage, the comparatively low figure of 7.52 was obtained. Similar but reciprocal changes in the Pco_2 were recorded; all but one case reached values of 23.5 mm Hg or lower, the lowest value recorded being 12.5 mm Hg and the highest being 27.5 mm Hg. A further description of the Pco_2 changes are given by Robinson (1960).

Pain response.

In all cases the pain response rose, the average increase in pressure required to elicit a response being 7 kg $\pm$ 2. In six subjects the rise was below the average and in eight it was above, but these readings could not be related to greater or lesser changes in pH values (fig. 2).

To demonstrate the direction and extent of the changes in pain response during hyperventilation, all the pain response and pH readings for the twenty subjects are presented as a semilogarithmic plot in figure 2. This includes the basal levels of pain response which show the usual trimodal distribution of normal, hyper- and hyposensitive responses. It was interesting to note that the obviously apprehensive subjects had high initial pH values, probably due to their emotional overventilation whilst awaiting the start of the experiments.

It can also be seen from figure 2 that the pain threshold rose with hyperventilation until pH values around 7.55 were reached. Further increases in pH above this value did not raise the pain threshold to any appreciable degree.

Inhalation of ammonia, amyl nitrite and oxygen.

The effect of the inhalation of concentrated ammonia vapour was the same in all cases. It caused an immediate fall in pain response which quickly returned to within 1 or 2 kilogrammes of the original value. Examination of the optic fundus at this time showed the retinal vessels to be maintaining the vasoconstriction.

The immediate effect of the inhalation of amyl nitrite was exactly the same as that of concentrated ammonia vapour. There was an immediate fall in pain response to levels within 1 or 2 kilogrammes of the pressure originally required.

The pain response was tested again at a time when the amyl nitrite had caused intense facial vasodilatation and dilatation of the retinal vessels but the blood pressure had returned to within 10 mm Hg of its initial value. At this time the pain response in eight subjects had returned to within 1 kilogramme of the pre-amyl nitrite level and in twelve instances it had increased above this level.

In all except two cases the administration of ammonia and amyl nitrite caused a disturbance in respiratory rhythm due to the irritant nature of the vapours. In three of the subjects estimation of the acid-base changes after inhalation of these vapours showed that there was a fall in pH value of between 0.1 and 0.08 pH units.

The administration of 100 per cent oxygen for 4 minutes caused no change in pain response or fundal vessels. Indeed, the only effect observed occurred in three subjects who became very sleepy during its administration.

Other cerebral changes.

All these subjects showed a diminution in mental agility. Simple mental arithmetical tests using figures of unity were performed slowly but correctly; however, problems involving figures over unity in most instances resulted in erroneous answers. Several subjects found that, although anxious to help by answering such questions, the problems were too involved for coherent thought.

All except one of the subjects commented on the fact that they felt "rather odd" and all showed an amiability similar to that of mild

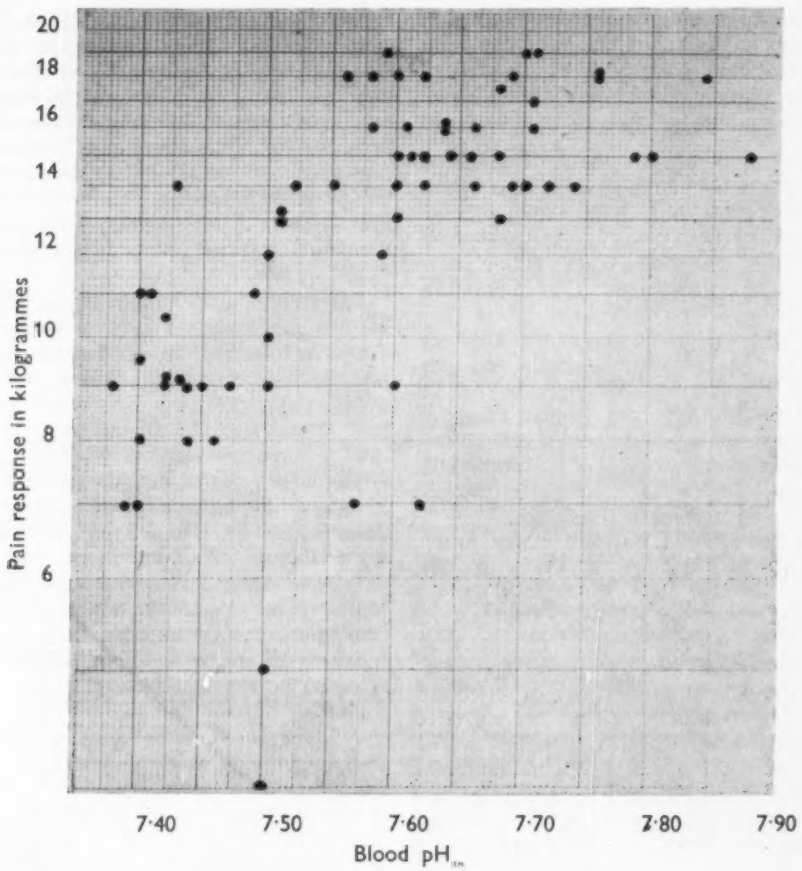

FIG. 2

Composite plot of pain response and blood pH compiled from values obtained before and during the experiments.
For clarity the pain responses have been plotted as log values although the flattening of the curve would be still evident on normal cycle graph paper.

alcoholic intoxication. Six subjects showed pronounced facetiousness and a tendency to hilarity.

The subjects were considered by a psychiatrist to have all their aggressive tendencies depressed. Furthermore, although on arrival in the laboratory for the experiments the volunteers were often apprehensive, towards the end of the experiment they became very co-operative and often volunteered spontaneously for further and even more traumatic experiments.

Visceral sensation.

A diminution in visceral perception seemed to occur. Three volunteers started the experiments with full bladders and all complained initially of an increased discomfort as the respirator applied intermittent pressure to the abdomen. After 10 to 15 minutes hyperventilation, when a respiratory alkalosis had been established, all three became unaware of bladder discomfort and it must be remembered that the experiments proceeded for at

least 1 hour. Acute vesical discomfort returned to these subjects within a short time of the cessation of hyperventilation.

DISCUSSION

It has been proposed that the cerebral effects accompanying a respiratory alkalosis are attributable to cortical hypoxia. This stems from the work of Kety and Schmidt (1946) who measured cerebral blood flow and oxygen uptake during active and passive hyperventilation. They found that the cerebral blood flow was reduced by one-third and that there was an increase in the difference between the oxygen tensions of arterial and cerebral mixed venous blood. Although they had no direct information, Kety and Schmidt suggested that the oxygen tension of the venous blood draining the cerebrum mirrored that of the cortical cells and that the observed fall in this value therefore indicated a degree of cerebral hypoxia.

Sugioka and Davies (1960) lent support to this suggestion by their findings that the oxygen tension in the cerebral cortex of dogs fell from a normal level of 8–15 mm Hg to 3–5 mm Hg when these animals were passively hyperventilated. These measurements were made using a modification of the Clarke (1953) oxygen electrode. Although the polarizing voltage was delivered intermittently at a rate of 8 pulses per second, since the work of Glover (1959) this rate must be regarded as too high and must have led to a rate of oxygen consumption at the electrode greater than that which could have been replaced by the diffusion of oxygen through the cortical tissues. For this reason, therefore, the figures for cortical oxygen tension produced by Sugioka and Davies would be too low and cannot be regarded as absolute values—they only indicate relative changes.

The lowest tension at which cortical tissue can utilize oxygen is not known, but further consideration of the work of Kety and Schmidt sheds some light on this subject. Their results show that during passive hyperventilation the oxygen uptake of the brain remained the same in spite of the great reduction in cerebral blood flow and the increase in cerebral arteriovenous oxygen difference. Furthermore, the results obtained during active hyperventilation show that the brain was able to increase its oxygen consumption, in spite of the reduced cerebral blood flow and greater cerebral arteriovenous oxygen difference. It is inconsistent to assume that cerebral hypoxia occurred during their experiments, because the oxygen consumption of the brain during passive hyperventilation was shown to be the same as the consumption at rest, yet, when an increased oxygen demand of the brain occurred as during the mental concentration necessary for active hyperventilation, this was satisfied by an increase in oxygen uptake.

The conclusion of Clutton-Brock (1957), that the analgesia produced by hyperventilation was due to cerebral hypoxia, was based upon the fact that in actively hyperventilating subjects the administration of oxygen lowered the pain threshold as did also the administration of a vasodilating substance—amyl nitrite.

The work reported here does not support the conclusion that the cerebral effects of hyperventilation are due to cerebral hypoxia for the following reasons.

In these experiments the adminstration of amyl nitrite, although causing an initial decrease in pain response, ultimately resulted in a considerable increase. An exactly similar initial decrease was achieved by the inhalation of strong ammonia vapour.

It is suggested that the initial lowering of the pain response to nearly normal levels after the administration of amyl nitrite and ammonia was due to the pungent nature of their vapours. This was, in fact, strong enough to cause disturbance of respiratory rhythm and consequent lowering of the pH and elevation of P_{CO_2}. These changes would in themselves result in some lowering of the pain response, but when considered in relation to the overall pain response/pH curve (fig. 2), it could be seen that they were insufficient to explain the return of the pain response to normal.

It seems more likely that the lowering of pain response with pungent vapours is due to a reflex stimulus of cerebral activity ("increased arousal") arising from its irritant action on the upper respiratory tract. It is presumed that this is much the same effect as that which "sal volatile" produced when prescribed for fainting attacks.

Furthermore, examination of the fundal vessels, which might be thought to reflect the reactions of the cerebral vessels, showed release of vasocon-

striction with amyl nitrite but maintained their vasoconstriction with ammonia. After the initial fall following amyl nitrite, the pain response returned to its former level or even higher although at this time the fundal vessels were still dilated and the blood pressure was within 10 mm Hg of normal. It seems unlikely, therefore, that there was any reduction in cerebral blood flow at this time despite the elevated pain response.

If cortical hypoxia is the cause of the raised pain response during hyperventilation, then oxygen inhalation might be expected to raise the oxygen tension of arterial blood and that of the cerebral cortex, thus reducing the analgesia. However, in these experiments, contrary to the findings of Clutton-Brock (1957), oxygen inhalation did not have this effect.

Finally, it was noteworthy that the other cerebral effects noted cannot be correlated with those known to accompany the hypoxia of high altitude flying. During high altitude flying headache, aggressiveness and over-confidence are predominant symptoms if cerebral hypoxia is present. The subjects of these experiments never experienced headache and, far from showing aggressive or reckless tendencies, became very co-operative and amiable.

If the cerebral effects of passive hyperventilation are not due to hypoxia they could be due to the high ambient pH of the cerebral blood flow, or the low Pco_2 level, but more likely a combination of the two factors.

Some support for this hypothesis is lent by the work of Bonvallet and Dell (1956) who showed that low carbon dioxide tensions produced by hyperventilation caused a marked decrease of the frequency of discharge from the reticular activating system and in certain animals caused complete depression.

CONCLUSION

The advantages of hyperventilation as an adjuvant to anaesthesia have been described by many authors and amongst the advantages claimed have been a reduction in the dosage of anaesthetic agents employed and an increase in their potency.

This investigation shows that these effects are probably due to the production of general analgesia and from the depression of other cerebral functions which results during passive hyperventilation. The suggestion that these effects are due to a reduction in cerebral blood flow and a degree of cerebral hypoxia is shown to be an hypothesis with little foundation. It is suggested that the cerebral effects can be accounted for by the changes in Pco_2 and pH values alone.

SUMMARY

Twenty male subjects were passively hyperventilated using a cuirass type of respirator. The pain response as measured by the application of a spring-loaded plunger to the tibia was shown to rise during hyperventilation until blood pH values of around 7.55 were reached.

It was suggested that as the retinal vessels probably behave in a similar manner to those of the brain, observation of them during the experiments, would give useful information. They were seen to constrict during hyperventilation. A fall in the elevated pain response was not demonstrated when vasodilation of the retinal vessels was produced by inhalation of amyl nitrite and when the blood pressure was at a normal level, nor did it fall during inhalation of oxygen. An initial decrease in pain response after amyl nitrite was noted and thought to be due to the irritant nature of its vapour as a similar effect was observed after inhalation of sal volatile.

Other cerebral effects observed were a loss of mental agility, a depression of aggressive tendencies, a loss of visceral sensation and the amiability characteristic of a mild alcohol intoxication.

As there was no decrease in analgesia with the production of retinal vasodilatation by amyl nitrite or by inhalation of oxygen it is considered unlikely that the cerebral effects are due to cerebral hypoxia resulting from the constriction of the cerebral vessels. It is suggested that the cerebral effects can be accounted for by changes in pH and Pco_2 values alone.

ACKNOWLEDGMENTS

We are indebted to the medical students (4th and 5th year in 1959) and those of our colleagues who volunteered to be the subjects of these experiments. We gratefully acknowledge the generosity of Technicon Instruments Co. Ltd. (London) who made available the very efficient pump cuirass.

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BOOK REVIEW

Anaesthetic Accidents (2nd edition). By V. Keating. Published by Lloyd-Luke, London. Price 28*s*.

This second edition is some thirty pages longer than the first. This increase in length and the revision of much of the text has been made desirable owing to the increasing interest that has been shown in the complications of anaesthesia since the publication of the first edition some five years ago. Dr. Keating admits that his limited experience of anaesthesia has not enabled him actually to be present at all the accidents that he describes and so he has had to supplement this deficiency by the experience of others. This has proved no detriment as he has made himself intimately acquainted with the reports of them sent to him. Indeed the outstanding impression of the book as a whole is the amount and quality of the thought that Dr. Keating has put into the consideration of his subject. There is a short chapter at the end dealing with medico-legal matters which will prove of immense help to the anaesthetist faced with the necessity of appearing in the coroner's court. From the point of view of accuracy a new proof-reader for the references is required.

E. Falkner Hill

Brit. J. Anaesth. (1961), **33**, 69

SOME BIOCHEMICAL EFFECTS OF PASSIVE HYPERVENTILATION*

BY

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FOR several years deliberate hyperventilation during controlled respiration, nitrous oxide, oxygen, relaxant anaesthesia has been practised by many anaesthetists. The advantages of this method have been discussed by Gray and Rees (1952), Rollason and Parkes (1957), Stephen and his colleagues (1958), and by Gray and Geddes (1959).

The use of hyperventilation as a supplement to light anaesthesia in place of potent analgesic and anaesthetic drugs has been criticized because of its alleged harmful effects. Of these supposed effects, the most injurious is that of cerebral hypoxia which has been discussed in a previous paper and its occurrence shown to be unlikely (Robinson and Gray, 1961).

Other effects which have been demonstrated and considered harmful during pulmonary hyperventilation are: tetany (Shock and Hastings, 1935); shift of the haemoglobin dissociation curve to the left; hypotension and peripheral vasoconstriction (Hewer, 1959); an increase in fixed acids and the production of a metabolic acidosis tending to compensate for the persistent elevation of pH (Papadopoulos and Keats, 1959; Hobsley and Nunn, 1959); changes in serum electrolytes (Brown et al., 1949); and a probable loss of plasma water (Balke, Ellis and Wells, 1958).

A clear distinction has not always been drawn between evidence from subjects who actively hyperventilated and those who were passively hyperventilated. Certainly much factual opinion on the biochemical effects of hyperventilation during anaesthesia was based upon evidence taken indiscriminately from both groups.

It must be stressed that the hyperventilation occurring during anaesthesia and with which this work is concerned is passive and does not involve muscular or cerebral work by the subject being hyperventilated.

All investigators who have made measurements of the work of breathing over a range of ventilations have found that the oxygen requirement of the subject per litre of ventilation increases enormously at the higher degrees of ventilation. For example, Neilson (1936) found the oxygen cost of ventilation at a minute volume of 10 litres per minute to be approximately 1 ml of oxygen per litre of ventilation, but at a ventilation of 50 litres per minute the oxygen cost was about 2 ml of oxygen per litre of ventilation. Otis (1954) in reviewing the work of other investigators pointed out that the curve relating energy requirements to ventilation was not a straight line but a curve of ever increasing slope. It would seem, therefore, that the biochemical effects of passive hyperventilation are likely to be very different from those of active hyperventilation. This will be particularly so in regard to any metabolic effects observed.

To learn more about the possibly harmful effects of hyperventilation during anaesthesia, it was decided to investigate the effects of passive hyperventilation both in conscious volunteers and in anaesthetized patients. The volunteers had not the muscular exercise of actively hyperventilating subjects and they had a normal renal function. The anaesthetized subjects on the other hand, might be regarded as having a reduced oxygen demand (Shackman, Graber and Redwood, 1951), a decreased carbon dioxide production (Petersen and Elam, 1958), a depressed renal function (Papper, 1953), and they were certainly respiring a percentage of oxygen above that of room air.

It was hoped that differences might be found between the two series which would help to elucidate the nature and the severity of these effects of hyperventilation during anaesthesia.

METHOD

In the first series of experiments twenty fit male volunteers of ages ranging from 21 to 43 years were passively hyperventilated for a period of 1 hour, using a thoraco-abdominal cuirass and a

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Technicon Huxley pump. This method has been more fully described elsewhere (Robinson and Gray, 1961).

In the second series, twenty-one cases, male and female, undergoing either appendicectomy or cholecystectomy, were deliberately hyperventilated during anaesthesia. Only those patients shown to have a normal acid-base balance before operation, as measured by the standard bicarbonate values, were included in this series. No patient had an intravenous infusion during the operation. All the patients were premedicated with morphine sulphate 10 mg and atropine sulphate 0.6 mg, 45 to 60 minutes before the start of the operation. The anaesthesia used in each case involved induction with tubocurarine and thiopentone followed by nitrous oxide, oxygen and hyperventilation for maintenance. In both series of experiments, arterialized venous blood (Brooks and Wynn, 1959) samples were drawn into heparinized syringes the deadspace of which had been filled with neutral mineral oil. Samples were taken before the start of the procedure and at 15-minute intervals.

The following investigations were carried out on these samples:

(1) pH. This was measured anaerobically at 38°C using a micro-flow glass electrode system (E.I.L.), and a Vibron Model 33B (E.I.L.) pH unit. The electrode cell was standardized using a phosphate buffer as a primary standard and this was itself checked using a borate buffer. The standard scale ascribed to these buffers was that described by Mattock (1959).

(2) Pco_2 and standard bicarbonate (Astrup, 1956) were estimated on anaerobically separated plasma using the method of Robinson and Pimblett (1961).

(3) Serum potassium and sodium were estimated with a laboratory-made flame photometer using lithium sulphate as an internal standard; serum chlorides were estimated using the method of Van Slyke and Hiller (1947) and plasma water by accurate weighing of known volumes of plasma before and after dehydration at 140°C for 14 hours, followed by cooling in a desiccator. Haematocrit values were obtained by centrifugation in Wintrobe tubes at 2,000 r.p.m. for 30 minutes.

(4) Pulmonary ventilation was measured at 15-minute intervals as expired minute volume using the anemometer described by Wright (1955).

RESULTS

Degree of ventilation achieved.

The pulmonary ventilation attained by the conscious subjects varied from subject to subject and varied from period to period in the same subject. The full details have been listed elsewhere (Robinson, 1960). Most subjects achieved values of 30 litres per minute or more, two subjects reaching the remarkably high figures of 50 litres per minute. In no case in this series was the ventilation lower than 17 litres per minute.

In seventeeen subjects it was found that, as the experiments proceeded, the subjects increased their ventilation values as they became adapted to the pump. However, three subjects showed a marked decrease.

In the second series—the anaesthetized subjects—the degree of pulmonary ventilation achieved was extremely variable. All the patients were ventilated so that the expired minute volumes were between 12 and 20 litres per minute, but the degree of ventilation varied erratically from patient to patient and also from instant to instant in the same patient. There were two reasons for these findings:

(*a*) The degree of ventilation obtained depended upon the compliance of the lungs and thorax of each individual. A low compliance was present in certain cases due to the physical characteristics of the patient; in others there was a low compliance due to inadequate relaxation of the muscles. The dosage of relaxant was kept low because the anaesthetist expected the surgical procedure to be short.

(*b*) The necessity for a quiet operative field sometimes led to a diminution in the degree of hyperventilation.

That hyperventilation was achieved in the anaesthetized patients is shown by the fact that all were ventilated at minute volumes over 12 litres per minute throughout. The mean ventilation for this series was 13.5 litres per minute and a maximum minute volume of 20 litres per minute was achieved in three patients.

pH and Pco_2 changes.

In the first series of experiments—those on conscious subjects—the method of hyperventilation caused a steep initial rise of pH and a fall in Pco_2 within the first 15 minutes. Thereafter the rate of rise and fall respectively of these values

became progressively slower. Six subjects showed little or no further changes after 45 minutes of hyperventilation.

With one exception, the method of ventilation employed caused a rise in arterial pH above 7.6, the average rise being to 7.69 units. In two subjects rather high pH values of 7.84 and 7.88 were recorded. Similar but reciprocal changes of arterial Pco_2 were recorded, all the subjects reaching values of 25 mm Hg or lower, again with the exception of one subject. The lowest values recorded were 15 and 12.5 mm Hg.

The small changes of pH and Pco_2 in the single subject were probably due to the poor ventilation values achieved due to the rigid barrel-shaped thoracic cage of this subject.

In the second series—the anaesthetized subjects—all showed a rise in pH and fall in Pco_2 from the basal values. The degree of respiratory alkalosis could in no way be correlated with the degree of ventilation. This was almost certainly due to the intermittent and periodic nature of the estimations of ventilation. The values of ventilation recorded did not represent a true state of affairs because between estimations, ventilation often varied erratically due to other necessary activities of the anaesthetist. The main purpose of the experiments was to achieve a state of respiratory alkalosis by overventilation and that this was achieved is shown by the fact that the mean arterial pH for the series was 7.52, with the lowest value recorded of 7.45 and 7.68 as the highest. The changes in Pco_2 were again similar but reciprocal, the mean value being 27.6 mm Hg with a lowest value of 18 mm Hg and the highest being 36 mm Hg.

The complete analysis of ventilation pH and Pco_2 changes for both series of experiments has been presented elsewhere (Robinson, 1960).

Metabolic changes (standard bicarbonate).

In the experiments performed on conscious subjects all but two showed a diminution in standard bicarbonate levels. An overall picture of the changes is shown in table I where the means of the values obtained in seventeen of the subjects and the means of their differences are listed. The "t distribution" test demonstrates that there is a significant fall of standard bicarbonate levels of more than 1.5 mM/l. and the standard deviation of the means shows the individual variation of the decrease in standard bicarbonate to be low.

In the anaesthetized subjects the standard bicarbonate was reduced in all but eight cases. Table II shows that there was a mean reduction of 0.805 mM/l. and that this was statistically significant. The small standard deviation of the mean reflects the findings that the standard bicarbonate fall was small.

Haematocrit and plasma water changes.

In the conscious subjects eighteen showed a rise in haematocrit value after hyperventilation, the mean rise being 3.6 per cent (S.D. 1.07; $P < 0.001$). In the anaesthetized patients there was also a small but definite increase in the haematocrit values the mean rise being 0.68 per cent (S.D. 0.067; $P<0.001$).

The changes in plasma water values for both series are set out in tables I and II. It can be seen that there was a mean fall of plasma water in the first series of 5.32 g/l. but there was a wide individual variation in the degree of loss of plasma water (S.D. 2.5). There was a very small fall in plasma water (0.334 g/l.) in the anaesthetized

TABLE I
Biochemical changes during passive hyperventilation. Series I

	No. of cases	Mean before hyperventilation	Mean after hyperventilation	Mean of the differences	Standard deviation of the mean of the differences	Significance of the means using t-distribution
Na^+	13	148 m.equiv/l.	143	−5.26	1.5	$P<0.01$
K^+	11	3.14 m.equiv/l.	2.98	−0.64	0.02	$P<0.01$
Cl'	12	104 m.equiv/l.	106	+1.65	0.949	$0.1>P>0.2$
Plasma water	17	939 g/l.	934	−5.32	2.5	$P=0.05$
Standard bicarbonate	17	24.4 mM/l.	23	−1.61	0.35	$P<0.001$

TABLE II
Biochemical changes during hyperventilation in anaesthesia. Series II.

	No. of cases	Mean before hyperventilation	Mean after hyperventilation	Mean of the differences	Standard deviation of the mean of the differences	Significance of the means using t-distribution
Na^+	6	148 m.equiv/l.	142	−5.67	0.478	$P<0.001$
K^+	7	3.26 m.equiv/l.	3.04	−0.20	0.065	$0.02<P<0.5$
Cl'	8	101.9 m.equiv/l.	102.7	−0.71	0.12	$0.5<P<0.6$
Plasma water	6	938.5 g/l.	938	−0.334	0.57	$0.5<P<0.6$
Standard bicarbonate	22	24.1 mM/l.	23.3	−0.805	0.19	$P<0.001$

subjects but the individual variation is very great (S.D. 0.57) and the results lack statistical significance.

Electrolyte changes.

The results obtained in each series are analyzed in tables I and II. In both the conscious and anaesthetized subjects there was a significant fall in the levels of serum sodium. The level of serum potassium fell significantly in the conscious subjects, but no significance can be attached to the results from the anaesthetized subjects. The changes in serum chlorides are random in both series and are without significance.

Tetany.

No tetany was seen in the anaesthetized subjects. Six subjects in the first series of experiments complained of tingling in the hands commencing about 15 minutes after the start of hyperventilation, but in all cases this stopped after 30 minutes' hyperventilation. One subject exhibited true tetany commencing within 5 minutes of the start of hyperventilation. A "main d'accoucheur" was produced in both hands and Chvostek's and Trousseau's signs were strongly positive. The tetany became so severe that the experiment was abandoned after 10 minutes of hyperventilation. This subject was found to have a low basal standard bicarbonate (20 mM/l.) and this dropped sharply to 18 mM/l. within the short time that hyperventilation was attempted.

It was obvious that this subject was incapable of allowing the respirator to ventilate him passively and appeared to be exerting some considerable effort to reach the values of ventilation recorded.

A subsidiary experiment was performed to ascertain the oxygen uptake of a similar subject who also proved incapable of allowing passively imposed hyperventilation. It was found that for a given degree of ventilation the oxygen uptake as measured by a spirometer trace was 70 ml O_2/min greater for attempted passive hyperventilation than for the same degree of active hyperventilation. Attempts to ventilate against the respirator required more muscular work than an equivalent degree of active hyperventilation.

A "main d'accoucheur" was seen in five subjects but this was not present in the hand being heated to obtain arterialized blood samples. The effect of heating the hand in spasm by warm air from an electric hair dryer was to relax the spasm as the hand was warmed.

Cardiovascular effects.

Nine subjects in the first series of experiments showed minor falls in systolic blood pressure of 5 mm Hg or less, two other subjects falling by 10 mm Hg. No blood pressure changes were noted in the anaesthetized subjects, as the absence of such changes was one of the criteria for inclusion in the series. All subjects in the first series exhibited some degree of peripheral vasoconstriction and in four subjects this was intense enough to cause the subjects to complain of cold and numbness of the extremities. No obvious vasoconstriction was observed in the anaesthetized subjects.

DISCUSSION

Ventilation achieved. An observation by Fenn et al. (1949) suggested that when a state of respiratory alkalosis has been produced a mechanism comes into play which possibly reflexly "stiffens"

the chest reducing the passively imposed hyperventilation.

This observation appears to be confirmed by the falling ventilation values found in three of these subjects but no conclusions as to the nature of this mechanism can be drawn.

pH and Pco_2 changes. The finding of several workers (Lepper and Martland, 1927; Shock and Hastings, 1935) that the maximum pH change occurs within 15 minutes of active hyperventilation was probably attributable to the increased production of carbon dioxide which resulted from the raised activity of the respiratory muscles during active hyperventilation, thus offsetting the effects of the increased ventilation. This is supported by the finding in this series of experiments that the pH of the blood continued to rise for at least 45 minutes, when the subjects were hyperventilated passively.

It is probable that the final limits of pH and Pco_2 changes are set by the ventilation/perfusion ratio of the subject's lungs. If the rate of change of alveolar gas exceeds the rate of change of the perfusing blood, then no further blood gas changes can occur and a steady state of arterial Pco_2 and pH will occur. It might be considered that the six subjects in the first series who showed little or no change in pH or Pco_2 after 45 minutes of hyperventilation had reached the limit set by the ventilation/perfusion ratio of their lungs.

The limit of elevation of blood pH compatible with life has been stated as 7.8 (Best and Taylor, 1955), yet one subject in the first series of experiments reached a pH of 7.88 and apparently did not suffer any ill effects. It is unlikely that a much higher arterial pH can be reached by either active or passive hyperventilation, as greater volumes of ventilation than those obtained in these subjects are probably very difficult, if not impossible, to achieve.

It would seem, therefore, that the maximum limit of blood pH, which it is possible to achieve by passive hyperventilation, would not result in serious ill-effects in healthy subjects.

Standard bicarbonate changes. In both series of subjects passive hyperventilation produced a metabolic acidosis as demonstrated by a fall in the values of standard bicarbonate. This was greater in the first series of subjects and can be attributed to the fact that these subjects had not been given a muscle relaxant and therefore they probably exerted some respiratory muscular effort. This would increase the amount of fixed acids in the blood and so lower the value of standard bicarbonate.

The suggestion that the respiratory alkalosis produced by hyperventilation during anaesthesia is completely controlled by the production of a metabolic acidosis, as suggested by Hobsley and Nunn (1959), is shown to be without foundation. No fall in blood pH was demonstrated with increasing duration of hyperventilation and the metabolic acidosis as measured by the fall in standard bicarbonate was small.

The degree of metabolic acidosis which has been shown to occur is small in conscious subjects and minimal in anaesthetized subjects. It is less than the metabolic acidosis which has been reported by Holaday, Ma and Papper (1957) following moderate respiratory acidosis and certainly less than the metabolic acidosis found to follow ether or cyclopropane anaesthesia by Bunker and his colleagues (1951). It is difficult to believe, therefore, that this metabolic change can be of clinical consequence during anaesthesia.

Haematocrit and plasma water changes. There is no doubt that passive hyperventilation in conscious subjects produced both an increase in the haematocrit value and a fall in the amount of plasma water. Although the haematocrit values were shown to rise in hyperventilated anaesthetized subjects no conclusions can be drawn as to the behaviour of plasma water in these subjects.

The results from the first series of experiments show that there was a loss of plasma water of the order of 0.5 ml/100 ml but the volume of red cells rose by 3.6 ml/100 ml of blood. It is obvious, therefore, that a loss of plasma water could not account for the increase in haematocrit values, which must therefore be due to an increase in the number of circulating red cells. This was confirmed when a pilot trial in four subjects did not show any increase in the mean corpuscular volume after hyperventilation.

Where these red blood cells come from is a matter for conjecture. It is difficult to conceive of a mechanism which could actually manufacture red blood cells at such a rate as to produce these rapid changes in haematocrit values. It might be considered that the red blood cells could be re-

leased from a hypoxic red bone marrow due to a reduction of blood flow as a result of vasoconstriction. However, examination of the peripheral blood in three of the conscious subjects failed to reveal a reticulocyte response and therefore did not support this hypothesis. It is unlikely that the cells could have come from stores of mature red blood cells in the bone marrow because of its rigid volumetric size and large fat content.

It seems more likely, therefore, that the increased number of circulating mature red cells comes from a redistribution from stores of such cells held in the reticulo-endothelial system. Whatever the mechanism causing the increase in the circulating red cells its only effect can be to increase the oxygen-carrying capacity of the blood and can hardly be considered harmful.

The mechanism causing the loss of plasma water has been suggested (Balke, Ellis and Wells, 1958) to be loss of water either into the tissues or from the alveoli. If the loss were from the alveoli of the lung, and there is evidence to suggest that with large volumes of ventilation water vapour loss can be quite large (Cole, 1953), then it is difficult to understand why the water is not made up from the large mass of tissue water. The transference of this water across the capillary walls would be assisted by the increased osmotic pressure of the capillary blood due to its concentration after loss of water. Further, it is known since the work of Ekstein, Hamilton and McCammond (1958) that hyperventilation causes a marked reduction in the venous pressure in the forearm veins. If this occurs in other peripheral veins, then the hydrostatic pressure at the venous end of the capillary must be reduced and this would again favour the inflow of tissue water into the capillary. Therefore to account for the loss of plasma water it must be postulated that the increased blood pH or lowered Pco_2 causes an increased permeability of the capillaries which allows a loss of plasma water into the tissues and this loss must be added to that lost from the pulmonary alveoli. However, these suggestions are speculative and the main fact of importance to the present investigation is that, although there is a loss of plasma water, it is of a very minor degree and does not appreciably reduce the circulating blood volume.

Electrolytes. The results demonstrate that passive hyperventilation causes a fall in plasma sodium levels and that the fall is approximately equal in both series of experiments. The fall is greater than that observed by Brown and his colleagues (1949) and is also greater than that found by Rapoport et al. (1946) in results they obtained from active hyperventilation experiments. This may be due to the greater degree of respiratory alkalosis obtained during the experiments performed in the present work.

Plasma potassium levels showed a small but significant fall in both series of experiments. This is opposite of the changes found during active hyperventilation in the experiments of Rapoport et al. (1946). The random changes of plasma chloride estimations are in agreement with the results of Rapoport et al. (1946).

Rapoport et al. were able to explain their results, which were similar to the results obtained in the present study, by postulating a shift of water from the red cell into the plasma in accordance with a Donnan equilibrium. This hypothesis is untenable in the light of the finding in the present work of a decrease in the water content of plasma and an increase in the packed cell volume without any change in the mean corpuscular volume.

It is very difficult to produce an adequate explanation to cover the result obtained in this investigation. The renal excretion is depressed during anaesthesia and also is likely to be too slow a process to explain the decrease in cations found in the conscious subjects.

To explain the loss of plasma water it has already been suggested that the capillary permeability is increased and it seems likely that this may account for a loss of plasma sodium and potassium as these cations may also pass into the tissue fluid. If this does occur, its mechanism requires further investigation.

Macphee (1953) confirmed that in man the metabolic response to surgery was associated with a loss of potassium and a retention of sodium. It is noteworthy that the loss of sodium found in the present experiments is much less than the retention found to occur by Macphee after operation. Provided, therefore, that plasma potassium loss is insignificant, as has been demonstrated, the electrolyte changes which are likely to occur due to hyperventilation during anaesthesia are of little consequence.

Tetany. The single subject in whom tetany was

demonstrated had a mild resting metabolic acidosis which quickly became more severe as attempts were made to hyperventilate him passively. The increase in the metabolic acidosis of this subject must have been due to an increase in fixed acids (lactic, citric and pyruvic) from the increased activity of the subject's respiratory muscles.

It is interesting that in the anaesthetized subjects the metabolic acidosis produced was small (less than 1 mM), and no tetany was demonstrated in this series.

These results can be adequately explained from the findings of Fanconi and Rose (1958) who demonstrated that although there was a slight increase in the total plasma calcium the ionized calcium fell in the actively hyperventilating subject. This fall in ionized calcium was accompanied by an increase of similar extent in the complexed calcium fraction of the plasma. They suggested that this rise of plasma complexed calcium was due to the increase of fixed acids which occurs during hyperventilation. These acids, like citrates, are able to complex calcium ions and so can reduce the level of ionized calcium which is a potent cause of tetany.

Cardiovascular changes. Early investigators concluded that hyperventilation caused a marked fall in blood pressure (Ewald, 1873). Later workers, Kety and Schmidt (1946) and Brown et al. (1948), were unable to demonstrate a fall of blood pressure during hyperventilation when this was passively imposed. The present work confirms that the respiratory alkalosis produced by hyperventilation does not of itself cause a fall in blood pressure. The marked peripheral vasoconstriction seen in the observations on conscious subjects was not a feature of the anaesthetized subjects.

CONCLUSION

The conclusion is, therefore, that the purported harmful biochemical effects of supplementing light anaesthesia with hyperventilation are either absent or negligible. Indeed such effects are greatly outweighed by the advantages attendant upon light anaesthesia with respiration deliberately controlled to a state of respiratory alkalosis.

SUMMARY

Passive hyperventilation in a series of conscious and anaesthetized subjects was shown to cause a mild metabolic acidosis, an increase in haematocrit, a loss of plasma water plasma sodium and potassium. Tetany was only shown to occur in the presence of a severe metabolic acidosis.

The changes are shown to be minimal and are considered unlikely to be of clinical significance.

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THE RESPIRATORY PATTERN AND CARDIAC OUTPUT*

BY

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WHERE anaesthetic supplies and anaesthetic machines are particularly expensive, the use of open drop ether is obviously desirable for anaesthesia for many surgical procedures. This, however, is inadequate for open chest work or for other situations in which control of respiration is desired. Sleep may be produced with thiopentone, analgesia may be obtained with pethidine, and curare will afford adequate relaxation. All these agents, however, depress respiration. A combination of these three drugs would be inexpensive and adequate for anaesthesia for open chest cases if adequate control of respiration were obtained. One of us (K.T.) has devised a small and inexpensive automatic respirator whose power is furnished by either compressed air or oxygen. This instrument has been in clinical use in South America for several years. The gas used for power is delivered to the lungs of the patient so that only one source of oxygen is required. The original model gave a positive pressure phase lasting 65 per cent of the respiratory cycle. The expiratory phase included a slight negative pressure. The mean positive pressure was quite low.

The original model was modified to give equal inspiratory and expiratory phases. The expiratory phase again ends with a slight negative pressure. Mean pressure is quite low.

Work by Hubay et al. (1954), and Maloney et al. (1953) with dogs, and by Allbritten, Haupt and Amadeo (1954) and Maloney and Handford (1954) clinically, showed that alternating positive-negative pressure had little advantage over intermittent positive pressure breathing in normal subjects. The same authors, however, demonstrated the advantages of alternating positive and negative pressure in hypovolaemic subjects. Testing of cardiac outputs using normovolaemic and hypovolaemic subjects was deemed necessary in view of the reports by the above mentioned authors. Both models of the Takaoka respirator furnish alternating positive and negative pressures. The effect of these two instruments on cardiac output of dogs forms the basis for this report.

METHODS

A comparison of cardiac output using the Takaoka respirators with that obtained using manual manipulation of a breathing bag was made. To rule out the possibility of changes in circulating blood volume due to possible sequestration of red cells, splenectomized dogs were used. The dogs were put to sleep with pentobarbitone, an endotracheal tube was inserted, and the cuffs inflated. Cardiac output was measured by the method of MacIntyre et al. (1951) whereby radioactive isotopes are injected into the peripheral circulation. The average dilution volume leaving the heart was analyzed by measuring the radio-activity of femoral arterial samples taken in succession. The limit of accuracy of this method has been found in this laboratory to be 3 to 5 per cent.

The order of using the two methods of artificial respiration and the time at which bleeding was done were varied in order to rule out any differences which might have been due to these factors. Two dogs were ventilated for 20 minutes with the respirator before the measurement of cardiac output was made. After this, manually controlled respiration using the usual operating room technique, and giving approximately the same minute volume of ventilation as used with the respirator, was carried out for 20 minutes. A rapid inspiration followed by a relatively long pause after expiration was employed. After 20 minutes of this type of respiration, measurements of cardiac output, pulse and blood

* A preliminary report of this material was presented at the Second World Congress of Anaesthesiologists at Toronto, September 6, 1960.

pressure were again made. The dogs were then bled 20 per cent of their original calculated blood volume and the procedures were repeated, first using 20 minutes on the Takaoka respirator followed by 20 minutes of manually controlled respiration. The time of blood removal was altered for the next two dogs. The procedure involved breathing for the animal for 20 minutes with the Takaoka instrument, making measurements, removing 20 per cent of the blood volume, and after another 20 minutes of the use of the respirator, repeating the measurements. The blood was then reinjected and the dog's respiration was controlled manually for 20 minutes. Cardiac output was measured. Twenty per cent of the blood was again removed; 20 minutes were allowed to elapse during which time manual respiration was carried out and measurements again were made. The experiments were the same for another three dogs except that manual respiration was used first and instrument respiration used later. Thus experiments were done with seven dogs using the original Takaoka respirator.

Ten additional dogs underwent similar experiments employing the modified Takaoka respirator rather than the original model. For six dogs, respiration was controlled first using the Takaoka instrument and manual respiration was used later. With four dogs, manual respiration was used first and the Takaoka respirator later. With all ten dogs, control measurements were made and the animals were bled before the next measurement. The blood was reinjected and another control obtained using the alternative type of respiration.

RESULTS

The figures in table I show that in normovolaemic animals cardiac output was quite similar when using either the original instrument (136 ml/kg/min) or when using manually controlled respiration (129 ml/kg/min). Removal of blood was followed by severe falls in cardiac output when the Takaoka instrument giving prolonged inspiration and short expiration was used (51 ml/kg/min). Cardiac output was only moderately lessened when manual control of respiration was available (110 ml/kg/min). The values obtained during the use of the modified Takaoka instrument do not show this marked difference between manual and instrument control of respiration. The drop in cardiac output when the dogs were rendered hypovolaemic (120 to 106 ml/kg/min) was not nearly so serious when the inspiratory and expiratory phases of respiration were equal.

DISCUSSION

Cournand et al. (1948) and Motley et al. (1948) have stated that for intermittent positive pressure breathing with a minimal disturbance of circulation, a respiratory pressure curve should show (*a*)

TABLE I

Cardiac output of splenectomized dogs.
Manual respiration compared with control by Takaoka respirator.

I. *Original respirator.* Inspiration is 65% of cycle.

Dog No.	Normovolaemic		Hypovolaemic	
	Manual control ml/kg/min	Respirator ml/kg/min	Manual control ml/kg/min	Respirator ml/kg/min
1	146	138	119	42
2	123	135	120	48
3	140	133	124	44
4	135	123	106	48
5	121	152	91	46
6	147	147	146	96
7	92	125	61	34
Average	129 A	136 B	110 C	51 D
SE_m	7.88	4.33	11.12	8.31

D is very highly significantly different from A, B and C.

TABLE I (*continued*)

II. *Modified respirator.* Inspiratory phase equals expiratory phase.

Dog No.	Normovolaemic		Hypovolaemic	
	Manual control ml/kg/min	Respirator ml/kg/min	Manual control ml/kg/min	Respirator ml/kg/min
8	95	85	85	80
9	125	133	118	128
10	150	143	143	135
11	125	119	113	106
12	122	131	134	113
13	90	85	95	90
14	163	154	158	150
15	56	48	41	49
16	151	154	90	96
17	142	147	119	115
Average	122*	120*	110*	106*
SE_m	11.02	11.91	11.18	9.67

* No statistically significant differences.

a gradual increase in pressure during inspiration, (*b*) a rapid drop in pressure after cycling occurs, (*c*) a mean mask pressure during the expiratory period as near atmospheric as possible and (*d*) an expiratory time equal to or exceeding the inspiratory time. The original apparatus devised by K. T. satisfied requirements *a*, *b*, and *c* reasonably well. The modified instrument satisfied requirement *d* in addition.

Confirmation of the results of some previous workers (Hubay et al., 1954; Maloney et al., 1953; Allbritten, Haupt and Amadeo, 1954; Maloney and Handford, 1954) was obtained in our experiments. Diminished cardiac output was observed during the experiments on hypovolaemic animals. It was observed that the hypovolaemic dogs which were ventilated by the original instrument, having a relatively long positive pressure phase, experienced a greater drop in cardiac output than they did when they were hypovolaemic and manually ventilated using a short positive pressure phase.

Use of the modified unit which has an expiratory phase as long as the inspiratory phase was followed by diminution of cardiac output in the hypovolaemic animals no greater in extent than that observed in the same dogs using manual respiration with a short inspiratory phase. In fact, the cardiac output was not significantly different from control values.

In their preliminary measurements, Motley et al. (1948) tested seven types of devices for the production of positive pressure. Of these, their "type-five" utilized alternating positive and negative pressure and had an inspiratory phase of 3.14 seconds with an expiratory phase of 2.75 seconds. The "type-five" instrument was quite similar to our original Takaoka respirator. In spite of this relatively prolonged inspiratory phase the instrument produced effects on the pH, Pco_2, carbon dioxide content, peripheral resistance and arterial oxygen saturation of the subjects tested which were at least as good as those produced with the other six types of instruments utilized. The cardiac output compared to that during spontaneous respiration was increased 1.9 per cent when the "type five" respirator was used. It decreased 10.8, 12.9 and 5.9 per cent respectively when using other positive pressure instruments. In spite of these data, Cournand et al. (1948) did not utilize this "type five" respirator in attempting to decide which might be the most desirable physiologically. They concluded that there is no evidence that negative pressure aids circulation, but the recommendations which they made were based on data obtained from healthy and presumably normovolaemic subjects. It would seem, therefore, that additional data might be obtained and examined in setting up criteria for an ideal respiratory pressure curve.

Some patients upon whom the original model was used showed cyanosis of the nail beds. Our results obtained with dogs indicate that this was

probably due to a diminished cardiac output. The use of the modified respirator has been quite satisfactory in this respect.

This instrument has been found to be more satisfactory for use in the ventilation of animals in laboratories than the commonly used windshield-wiper type instruments because it will not "stick" and does not throw oil into the lungs of the subjects.

SUMMARY

An instrument powered by compressed air or oxygen has been devised for controlling respiration. The gas used for power furnishes oxygen for the patient's lungs. Alternating positive and negative endotracheal pressures are produced. The earlier model had an inspiratory phase lasting 65 per cent of the respiratory cycle. In the later model the inspiratory phase is equal in length to the expiratory phase.

Cardiac output determinations have been carried out using these two models in experiments with splenectomized dogs. These were compared with the results obtained in situations in which respiration was manually controlled by intermittent pressure on a breathing bag.

The use of the earlier model resulted in cardiac outputs comparable with those obtained using manually controlled respiration when normal dogs were used. When hypovolaemic animals were used the cardiac output was diminished to a greater extent with the respirator than with manual control.

The use of the modified respirator, which produces equal inspiratory and expiratory phases with negative pressure at the end of the expiratory phase, resulted in cardiac outputs equivalent to those obtained by manual control of respiration, whether the dogs were normovolaemic or hypovolaemic.

The types of respiratory patterns which are most suitable for the maintenance of the optimum cardiac output have not been completely explored.

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THE RECENTLY INTRODUCED RAPIDLY-ACTING BARBITURATES; A REVIEW AND CRITICAL APPRAISAL IN RELATION TO THIOPENTONE

BY

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"THIOPENTONE is a well tried and reliable drug . . . to displace such a drug, a new compound must have clear cut advantages and should be assessed in the light of the hazards inherent in thiopentone". (Dundee, 1958.)

Since its introduction into clinical use 25 years ago, thiopentone has held pride of place amongst intravenous anaesthetics. However, during this time a search has gone on for more satisfactory compounds and judging by the number of reports in the literature, this search has been intensified in recent years. Much attention has been focused on nonbarbiturate compounds which, up to the present, have not offered serious competition to the barbiturates.

In this publication it is proposed to review the barbiturates which have been recently introduced into anaesthetic practice and those compounds which have been subjected to clinical trial, even though they have not proved suitable for everyday use.

It is first necessary to consider how thiopentone falls short of the ideal intravenous anaesthetic and then to see if any of the newer compounds overcome these deficiencies. It is also important to compare the toxicity of the newer compounds with that of thiopentone with awareness that any possible advantages they may have over the standard drug must not be "bought at too great a price".

UNDESIRABLE ACTIONS OF THIOPENTONE

It should be emphasized that many of the hazards associated with the use of thiopentone are due to a rapid onset of anaesthesia rather than to a specific action of this particular drug; such dangers as vomiting and regurgitation are probably present to the same extent with any rapidly-acting intravenous agent. The hazards associated with the use of thiopentone in porphyrics seem to be shared by all barbiturates and it is expected that this will apply to conditions in which undue sensitivity to the drug is manifest.

From the point of view of the practising anaesthetist the following seem to be inherent dangers associated with thiopentone.

Local irritation of tissues.

Perivenous injection can produce intense pain and even sloughing of subcutaneous tissues, depending on the concentration and volume of misplaced solution. The sequelae of intra-arterial injection can include nerve lesions, tissue damage and even gangrene of the limb. While these are minimized by the use of dilute solutions this necessitates the injection of greater volumes and the use of larger and more clumsy syringes.

Cardiovascular depression.

While this can be lessened by the slow injection of dilute solutions, it is an inherent toxic action of the drug which cannot be ignored.

Respiratory depression.

This likewise can be minimized by proper use of the drug, but its augmentation by opiate premedication is not always appreciated.

Other undesirable respiratory effects.

These include coughing, hiccough, laryngospasm, sneezing and bronchospasm which fortunately occur very rarely.

Lack of analgesia.

This limits the safe employment of the drug as the sole narcotic except for brief procedures.

Delayed recovery of consciousness and cumulative action.

Whether or not this is a disadvantage depends on the nature and duration of the operation and the part played by the drug in the anaesthetic

technique. When used as a basal narcotic for the induction of anaesthesia for major operations the duration of action of moderate doses of thiopentone seems ideal. If a drug with a more rapid rate of recovery is used it may be necessary to revise many of our standard anaesthetic techniques to ensure a more rapid uptake of volatile and gaseous anaesthetics. However, for minor procedures, particularly on outpatients, the delayed recovery is a disadvantage. Irrespective of the circumstances attendant on its use, full return of mental faculties may be delayed for several hours.

Failure to produce muscular relaxation in safe doses.

With modern anaesthetic techniques this is not a major disadvantage of thiopentone and a drug which produces greater relaxation may well cause a greater degree of respiratory depression.

MODIFICATIONS OF THE BARBITURATE NUCLEUS

It is necessary next to consider those sites at which the barbiturate nucleus can be modified to produce compounds of use in anaesthesia (fig 1). This subject has been discussed at great length in the publications of Tatum (1939, 1940); Raventós (1954) and Richards and Taylor (1956) and is mentioned to explain the classification used in this review. The sites of substitution are as follows:

1. This is normally a hydrogen atom, which can be replaced by methyl or ethyl group. These changes frequently produce compounds with a more rapid recovery rate but they may have convulsant properties.

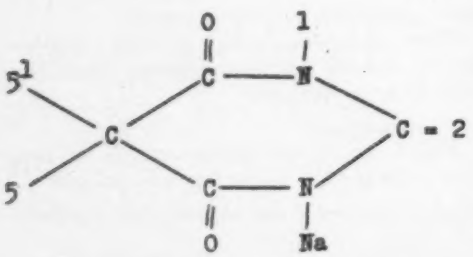

FIG. 1

Sites of modification of the barbiturate nucleus.

2. The substitution of a sulphur for an oxygen atom in this position produces compounds with an appreciably shorter duration of action. This is sometimes erroneously attributed to more rapid detoxication whereas alteration in distribution in the body plays the main part. In the case of pentobarbitone (O) and thiopentone (S), the onset of anaesthesia with the latter drug is more rapid (Dundee, 1957) and equilibration with brain tissue occurs more quickly (Mark et al., 1958; Goldstein and Aronow, 1960). The degree of plasma binding is greater with the sulphurated compound, which also has a greater affinity for fat (Brodie, 1952). It has been stated by Cope and Hancock (1939) and Knoefel (1945) that conversion of a barbiturate to a thiobarbiturate makes stimulant properties appear frequently. Richards (1951) however, has observed a marked species difference in this effect.

5 & 5¹. These have been the most popular sites of attack by research chemists and substitution has been with aliphatic, aromatic or heterocyclic radicals as well as halogenated and sulphurated aromatic radicals. Optimum results seem to be achieved with one short and one long chain substituent, containing from 4 to 8 carbon atoms in toto. Double bonds (allyl, pentyl) produce compounds which are more vulnerable to tissue oxidation and may be shorter acting.

For the purpose of this review, the drugs have been divided into four groups as follows:

1. Oxybarbiturates. 2. Methylated oxybarbiturates. 3. Thiobarbiturates. 4. Methylated thiobarbiturates.

Most of the compounds which are either in clinical use or have been subjected to clinical trial are listed in table I. Another group, the spiro-thiobarbiturates is not included above but is mentioned for the sake of completeness.

A graphic representation of the side chains of the drugs to be discussed in detail is given in figure 2. It can be seen from this figure and table I that the number of radicals in the 5 and 5¹ positions of the various drugs is not very great and thus the differences to be expected between some of the compounds cannot be marked.

An attempt has been made to assess the

TABLE I

Classification of various barbiturates, according to changes in the 1 and 2 positions of the side chains and their approximate potency relative to thiopentone.

Group	Drug	Side chains 1	2	5	5′	Approximate induction potency compared with thiopentone
1	Pentobarbitone	H	0	Ethyl	1-methyl-butyl	1.0
	Amylobarbitone			Ethyl	2-methyl-butyl	0.5
	Quinalbarbitone			Allyl	1-methyl-butyl	1.0–1.2
2	Hexobarbitone	CH_3	0	Methyl	Cyclohexenyl	0.5
	Narconumal			Allyl	2-methyl-butyl	1.0
	Narcodorm: Narkotal			Bromallyl	2-methyl-butyl	0.75
	*Methohexital			Allyl	1-methyl-2-pentynyl	2.5–4.0
3	Thiopentone	H	S	Ethyl	1-methyl-butyl	1.0
	Thiamylal			Allyl	1-methyl-butyl	1.0–1.2
	Thialbarbitone			Allyl	Cyclohexenyl	0.5
	*Inactin			Ethyl	1-methyl-propyl	0.7–0.8
	*Buthalitone			Allyl	2-methyl-propyl	0.5
	*Methitural			Methyl-thioethyl	1-methyl-butyl	0.6–0.7
4	Methyl-thiopentone	CH_3	S	Ethyl	1-methyl-butyl	
	Methyl-thiamylal			Allyl	1-methyl-butyl	
	*B.137			Ethyl	1-methyl-propyl	0.7–0.8
	*B.82			Allyl	2-methyl-propyl	0.5

* Only these drugs are reviewed in this publication.

Approved name	Other names	Side chains 1	2	5	5′
Methohexital	Lilly 25398 Brevital Brietal	CH_3	0	$CH_2=CH-CH_2$	$H_3C_2-C\equiv C-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-$
Inactin		H	S	H_3C_2-	$CH_3-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-$
Buthalitone	Transithal Ulbreval Baytenal	H	S	$CH_2=CH-CH_2-$	$\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\diagdown}}CH-CH_2-$
Methitural	Neraval Thiogenal Methothiouralt	H	S	$CH_3-S-CH_2-CH_2-$	$CH_3-CH_2-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-$
B.137		CH_3	S	H_3C_2	$CH_3-CH_2-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-$
B.82		CH_3	S	$CH_2=CH-CH_2-$	$\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\diagdown}}CH-CH_2-$

FIG. 2

Graphic representation of side chains.

relative potency of induction doses, as compared with thiopentone, in table I. Since all workers are not unanimous in their opinions on this subject, most of the values quoted are based on the authors' own experiences with the drugs.

Published reports frequently give different values for the pH of the same drug in the same concentration, presumably due to different methods of measurement. Table II lists readings obtained by the authors at room temperature using the same apparatus for all drugs. Since all are strongly alkaline, it is to be expected that the incompatibilities which Dundee (1956) gives for thiopentone will apply to all the drugs under review.

TABLE II

pH of various strengths of solution at 19°C.

Drug	Strength of solution			
	1%	2½%	5%	10%
Hexobarbitone		11.05	11.39	11.50
Narconumal		10.70	10.82	10.93
Narcodorm			9.95	
Methohexital	11.11	10.95	11.03	
Thiopentone		10.81	10.81	
Thiamylal		10.60	10.52	
Thialbarbitone		10.25	10.30	10.40
Inactin		10.50	10.50	
Buthalitone		10.60	10.55	10.47
Methitural		10.42	10.42	10.40
B.137		11.25	11.30	
B.82		10.55	10.55	

Claims are frequently made as regards the more rapid onset of a particular preparation. Using reactive hyperaemia to produce maximum forearm blood flow (Dundee and McArdle, 1959) the authors have found that adequate doses of all drugs to be discussed later can cause loss of consciousness within one arm-brain circulation time.

Each drug will now be discussed in the order set out in figure 2, and consideration will be given to their merits and demerits, using thiopentone as the standard.

METHOHEXITAL

History.

This compound was first described by Stoelting in 1957. Previous studies with a similar compound (Lilly, 22451) had shown that it was more potent than thiopentone and that recovery was more rapid (Chernish et al., 1956). However, this drug was found to have undesirable convulsive properties, but was fractionated into low and high melting point isomers, the latter being methohexital (Redish et al., 1958).

Physical properties.

Methohexital is a white crystalline powder, readily soluble in water, the aqueous solution remaining stable for at least six weeks at 25°C. It is distributed in bottles containing 500 mg to which has been added 30 mg of anhydrous sodium carbonate.

Pharmacology and toxicology.

Animal experiments by Stoelting (1957) showed methohexital to be about three times as potent as thiopentone. The duration of narcosis was only half as long as with thiopentone and the drug was less likely to show cumulative effects. The electroencephalographic patterns of cerebral depression were similar for methohexital and thiopentone. Chronic experiments demonstrated no pathological changes attributable to the drug.

Clinical reports.

The publications of Stoelting (1957), Reddish et al. (1958), Wyant and Chang (1959) and Taylor and Stoelting (1960) all confirmed the greater potency of methohexital as compared with thiopentone. The drug has been used in a 0.1–0.2 per cent continuous infusion and by intermittent dosage in one and two per cent solutions. In over 3,000 administrations Taylor and Stoelting found no thrombophlebitis during the postoperative period following the use of solutions not exceeding one per cent strength. The authors cannot confirm this finding when a two per cent solution has been employed but inadvertent subcutaneous injection of up to 100 mg produced no sequelae. Weyl et al. (1958) also noted this lack of local irritation following extravenous injection.

In the largest published series of cases 60 per cent of patients complained of pain at the site of injection or along the course of the vein. The intensity of the pain varied, but usually evoked a spontaneous and bitter complaint from the patient (Taylor and Stoelting, 1960). It is surprising that this complication has not been mentioned in any other publication, particularly in that of Wyant and Chang (1959) who used

methohexital as sole narcotic and whose observations were obviously made with great care. In a series of over 600 administrations by the authors and colleagues there has been no complaint of pain following the use of a two per cent solution in doses up to 950 mg.

All workers are agreed that recovery from methohexital is more rapid than after equivalent doses of thiopentone. Friedman (1959), using the drug for electroconvulsive therapy, found that treated patients could go home or return to work in about half the time noted for other barbiturates. In studies with volunteers Wyant, Dobkin and Aasheim (1957) noted the absence of "hangover" following methohexital as compared with other drugs. This was also the finding in a series of minor gynaecological procedures in which either methohexital or thiopentone was used as sole narcotic (Wyant and Chang, 1959). Using a "blind" technique and combining the barbiturate with nitrous oxide-oxygen for the operation of dilatation and curettage, Wyant and Barr (1960) have again confirmed the more rapid rate of recovery from methohexital. It has been frequently suggested that the drug would be very suitable for outpatient anaesthesia in view of this rapid recovery and absence of hangover but, up to the present, no study of this aspect of its use has been published.

Opinions vary somewhat as to the incidence and seriousness of complications following induction with methohexital. Stoelting (1957) noted only one instance of coughing and one of laryngospasm in his initial series of 285 patients. In the more recent paper, dealing with 3,340 administrations Taylor and Stoelting (1960) reported a one per cent incidence of spontaneous coughing and a slightly lower incidence of laryngospasm but about three per cent of patients had hiccoughs following induction. Compared with these low figures there was a 41 per cent incidence of hiccough reported by Wyant and Chang (1959), but it must be appreciated that these authors used the intravenous agents as the sole anaesthetic agent and that they found a 12 per cent incidence with thiopentone. In a further study, when these drugs were combined with nitrous oxide-oxygen (for the same operative procedures) hiccough did not occur in 55 patients (Wyant and Barr, 1960).

Muscle movements and tremor following induction are other complications about which reports are at variance. While not originally observed by Stoelting (1957) there was an incidence of approximately 3 per cent in the larger series reported by Taylor and Stoelting (1960). It was found that additional amounts of methohexital controlled these abnormal movements. A low incidence was also reported by Weyl et al. (1959) and Redish et al. (1958) while they did not occur at all in the series reported by Wyant and Barr (1960). However, the use of methohexital as sole narcotic for dilatation and curettage resulted in a 35 per cent incidence of minor muscle movements while 4 per cent of patients exhibited gross movements.

Many of the differences reported in the various publications may well be due to factors such as the strength of solution, the rate of injection, the dosage and the pre-anaesthetic medication. This latter has been studied in detail by Moore and Dundee (1961), who found that premedication with pethidine significantly reduced the incidence of muscle movements following injection while promethazine increased the incidence and severity of this complication to an alarming degree.

With a drug of the potency of methohexital, it is not surprising to find respiratory depression and apnoea mentioned as frequent complications of the induction, particularly following opiate premedication (Eckenhoff and Helrich, 1958). Dobkin and Wyant (1957) found a very high incidence with large doses, while Weyl et al. (1958) reported these complications in only 2 per cent of patients. The incidence and severity differs greatly in other publications and in the absence of dosage/incidence ratios no conclusions can be drawn.

Cardiovascular depression has not been a feature of the reports on methohexital and when hypotension has occurred it has been transient. More data is needed on this aspect of its action.

As well as the special indications which may arise from its brevity of action such as dental and outpatient procedures, Taylor and Stoelting (1960) consider methohexital to be eminently suitable for asthmatics. Weyl et al. (1958) found a slow infusion to be particularly useful for cardiac catheterization. If its lack of depressant

action on the cardiovascular system as compared with thiopentone is confirmed, it may well become the drug of choice in the elderly hypertensive subject.

Comparison with thiopentone.

Dundee and Moore (1961) have compared the actions of the two drugs as main narcotics for a standard operation. While agreeing with other workers that recovery from methohexital occurs more rapidly than after a comparable dose of thiopentone, they found that the course of anaesthesia was less smooth, particularly in the absence of opiate premedication. The frequency and severity of complications following induction was not such as to cause any anxiety and was more than compensated for by the minimum effects on the cardiovascular system as compared with thiopentone.

INACTIN

History.

Though originally described in the same publication as thiopentone in 1935 by Tabern and Volwiler, Inactin was not introduced into clinical practice until 1952 by Horatz and Sturtzbecher. Its pharmacology was extensively studied by Nieschultz (1953) and until the recent comparison of the action of Inactin with that of thiopentone by Dundee and Riding (1960) its clinical use in this country had not been reported.

Physical properties.

This drug is a yellow crystalline powder with a similar solubility and alkalinity to thiopentone.

Pharmacology and toxicity.

Tabern and Volwiler (1935) found that, in rabbits, the AD_{50} was 15 mg/kg as compared with 10 mg/kg for thiopentone; the relative values for LD_{50} being 50 mg/kg and 40 mg/kg respectively. This shows that Inactin has a slightly lower therapeutic ratio than thiopentone but the importance of this difference is doubtful in anaesthetic practice.

Block (1956) has studied the effect of single and repeated doses of Inactin on fat metabolism and hepatic function. He found no evidence of fatty infiltration of the liver during chronic Inactin intoxication and concluded that in the normal administration of Inactin to humans there is no indication that liver damage results.

Clinical.

With one exception, all the clinical reports on this drug have been published in the German language. These show the drug to be very similar in action and duration to thiopentone.

Comparison with thiopentone.

A detailed comparison of Inactin and thiopentone, involving almost 1,000 administrations of each drug, has recently been published by Dundee and Riding (1960). This confirmed the similarity between the two drugs as regards incidence of side effects and duration of action. The only difference of note was the lower potency of Inactin. The findings have been further confirmed by Dundee, Barron and King (1960) who used the drugs as main narcotic for a standard operation.

It is interesting to note that the above two publications show the effect of opiate premedication in reducing the incidence of muscle movements following thiopentone and Inactin. However, this effect is less striking than that noted by Moore and Dundee (1961) with methohexital.

BUTHALITONE

Like Inactin, although only comparatively recently introduced into clinical practice, buthalitone has been synthesized for over 25 years (Miller et al., 1936). Helmuth Weese, who introduced the first rapidly-acting barbiturate, hexobarbitone, into anaesthesia, was also concerned with its "rediscovery" (Weese and Koss, 1954) and Nobes (1955) first described its use in this country.

Physical properties.

These are again similar to thiopentone, but the solution is less stable and should be freshly prepared before use.

Pharmacology and toxicology.

Most of the reported studies have been concerned with the duration of action of buthalitone as compared with other drugs. Weese and Koss (1954), working with dogs, found that although the duration of anaesthesia with equipotent doses of hexobarbitone and buthalitone was similar, complete recovery occurred more promptly with buthalitone. This finding was substantiated by an uncontrolled study in man.

A large number of clinical observations suggested that buthalitone was a shorter acting anaesthetic

than thiopentone but it is only recently that these claims have been examined in detail. While Henderson and Mackett (1958), Keéri-Szántó and Labarre (1957) and Murray (1957) all studied the relative potencies of the two drugs in man and concluded that thiopentone was approximately twice as potent as buthalitone, O'Mullane (1957) found that at this ratio buthalitone produced a lighter level of anaesthesia as measured by the electroencephalogram. When doses of the two drugs were given which produced comparable patterns recovery of the normal pattern was slower with buthalitone than with thiopentone. This author suggests that buthalitone may give a false impression of brevity of action because the depth of anaesthesia as measured by the electroencephalogram is not as deep as is obtained with what are considered to be equipotent doses of thiopentone.

Using the patient's ability to obey verbal commands and to rise unaided to the sitting position as the criteria for recovery, Simmons and Blanchard (1957) were unable to demonstrate any difference between thiopentone and buthalitone. In a recent study, using a more complicated technique for determining the time of complete recovery Simmons and Curwen (1960) found no statistically significant difference between buthalitone and thiopentone.

Acute and chronic toxicity studies in animals by Weese and Koss (1954) and Vollmer and Haaf (1954) failed to reveal any deleterious effects of buthalitone as compared with other intravenous barbiturates. Evidence suggests that the drug is broken down by the liver.

Clinical.

From the above it is to be expected that much of the published clinical data concerns the use of buthalitone in minor surgery. Thus we have the reports of Drummond-Jackson (1956), Young (1956) and Mostert and Durham (1957) who used the drug in dental surgery, either alone or prior to nitrous oxide. These writers were all impressed with the smoothness of anaesthesia, the rapid uncomplicated recovery and the almost complete absence of hangover. On many occasions patients were able to leave the surgery unaccompanied within 30 minutes of operation.

Following the recommendation of Weese and Koss (1956), a number of authors including Ruddell (1955), Davidson and Love (1956), Guldmann (1956), Duffield and Ginsberg, (1957), Henderson and Mackett (1958) and Thoren and Matteson (1957), have used buthalitone as the main anaesthetic for minor operations. In many instances, the subjects were ambulant outpatients. Operations included incisions of abscesses, dressings, manipulation and reduction of fractures, endoscopy, external version and dilatation and curettage. Without giving much detail as to dosage, these workers are unanimous as regards rapidity of recovery and absence of hangover following is use. However, they are not all agreed on the incidence of complications during anaesthesia. Duffield and Ginsberg (1957), encountered a 31 per cent incidence of coughing while Guldmann (1956) considered that the incidence of respiratory upset was so high that he could not recommend the drug for general clinical use.

An interesting method is the "closed-vein" technique described by Davidson and Love (1956) a dose of 50 mg per stone body weight was used (maximum 500 mg). This produced a brief period of deep anaesthesia from which recovery was fairly rapid.

Little and Reid (1957) studied the use of buthalitone in electroconvulsive therapy and claimed that recovery was more rapid than after thiopentone. They also found that the respiratory depressant action of suxamethonium was antagonized by buthalitone. This has not been reported by McCall (1955) or Murray (1957) who also used the drug for electroconvulsive therapy.

None of the many clinical papers which deal with the use of buthalitone in major surgery have reported any findings of note. There is frequent reference to a rather high incidence of respiratory disturbances (coughing, hiccough, sneezing) and there are no claims that the drug is in any way superior to thiopentone.

Comparison with thiopentone.

As stated above, buthalitone is about half as potent as thiopentone as an induction agent and recovery from equipotent doses of the two drugs is similar. Judging from the fact that the drug does not seem to have displaced thiopentone to any extent in clinical use, it can be assumed that

it has not proved as satisfactory as the original drug.

METHITURAL

History.

This preparation was described by Zima, von Werder and Hotovy in 1954 and in the same year its pharmacological actions were reported by Dietmann. Reifferscheid and Dietmann (1954) first described its clinical use and all the early studies were carried out in Germany, where the drug is known as Thiogenal. In 1956 Irwin and his colleagues reported on studies carried out with the drug in America (proprietary name—Neraval) and its clinical use in the United States was first described by Boone, Munoz and Dillon (1956). The use of methitural in anaesthesia was mentioned frequently in American literature during the next three years, but Neraval is no longer commercially available. Apart from a brief report by Dundee (1956), methitural does not appear to have been used extensively in this country.

Physical properties.

Methitural differs from the other drugs in this review in that it contains a second sulphur atom in the alkyl side chain. Its chemical properties are similar to those of thiopentone but the aqueous solution is unstable and should be used within 24 hours of preparation.

Pharmacology.

Early workers considered the methyl-thioethyl radical (which is also present in the essential amino acid methionine) to be of great significance in the rapid detoxication and elimination of the drug as well as "protecting the liver" (Zima, von Werder and Hotovy, 1954). Dietmann (1954) found that in mice the total duration of narcosis with methitural was about half of that which followed doses of thiopentone producing an equal depth of anaesthesia. He also noted that it had less chronic toxicity than thiopentone. Irwin et al. (1956), however, found no significant difference in the time taken for recovery from small doses of methitural and thiopentone but with increased dosage recovery from methitural anaesthesia was significantly quicker than from thiopentone in the cat, dog and monkey. They also compared the cumulative action of equivalent doses of methitural, thiopentone and thiamylal and found that this was considerably less in the case of methitural than with the other two compounds. These workers found methitural to be about two thirds as potent as thiopentone.

The studies of Blake and Perlman (1956) showed that, like thiopentone, methitural was rapidly absorbed into body fat and that degradation occurred in the liver. No unchanged drug was found in the urine. Irwin et al. (1956) found that the affinity of the drug for fat was similar to that of thiopentone and they attributed the rapid recovery to an accelerated destruction, particularly in the liver. It is of some significance that these workers noted that methitural caused a higher incidence of tremors, abnormal muscle movements and coughing than thiopentone in animals.

On studying the effects of the drug in volunteers, Reifferscheid and Dietmann (1954) found that the potency of methitural was similar to that of hexobarbitone and appreciably less than that of thiopentone. They confirmed the animal observations reported above and concluded that recovery from methitural was more rapid than from either of the other two drugs.

Clinical.

Reports on the use of methitural in anaesthesia vary from the well controlled studies of Gale (1957) and Wyant, Chang and Aasheim (1958) to a large number of miscellaneous clinical observations whose sole merit is enthusiasm over the virtues of a new drug. It is proposed to discuss only the most useful of the publications.

O'Herlihy et al. (1956), using the drug for the operation of dilatation and curettage, were unable to demonstrate any shorter recovery time compared to thiopentone but they were able to demonstrate a shorter recovery time for methitural after a single hypnotic dose. Using the same operative procedure Gale (1956) could not detect any marked difference between the time for recovery between thiopentone and methitural and the study of Wyant, Chang and Aasheim (1958), carried out under almost identical conditions confirmed this finding. Similar conclusions were reached by Little, Creteur and Tovell (1959) in a study of recovery times following electroconvulsive therapy and by Egbert, Sechzer and Eckenhoff (1958) when the drugs were used for hypnosis.

Gale (1956) and Wyant, Dobkin and Aasheim (1957) and Egbert, Sechzer and Eckenhoff (1958) found that methitural caused a higher incidence of coughing, hiccough and laryngospasm than thiopentone. The frequency of these complications are also commented on by Fleming and Robinson (1957) and by Smith (1957).

Fitzpatrick, Clarie and Mersch (1959) noted that the injection of 10 per cent solution frequently caused pain and was often followed by venous thrombosis. This high concentration does not appear to have been used by other workers and there is no reason to suppose that a 2.5 or 5.0 per cent solution has more deleterious effects than the same concentration of thiopentone.

Comparison with thiopentone.

The dose of methitural required to produce sleep is about half as great again as that of thiopentone. The rate of recovery from equipotent doses of the two drugs is similar but methitural causes a significantly higher incidence of respiratory side effects.

B.137 AND B.82

These drugs were the most promising of a large series of N-methyl and N-ethyl substituted thiobarbiturates described by Peel et al. (1959). From figure 1 it can be seen that B.137 is the N-methylated form of Inactin whilst B.82 bears a similar relationship to buthalitone.

Barron, Dundee and King (1960) found that B.137 caused a significantly higher incidence of tremor and spontaneous involuntary muscle movement than thiopentone. It was interesting to note that the incidence of this complication increased with dosage. In a further study, in which the drug was also compared with Inactin, Dundee, Barron and King (1960) confirmed these findings and also showed that the incidence of side effects was markedly reduced by opiate premedication. B.137 and Inactin appeared to be equipotent and there was no evidence to suggest that methylation of Inactin produced a compound from which recovery occurred more rapidly.

In a small series of observations with B.82, Barron and Dundee (in press) found that the incidence of tremor, muscle movements, coughing and hiccough was prohibitively high and that injection of the drug was frequently followed by a generalized erythematous rash.

It is the opinion of the authors that neither B.137 nor B.82 has any place in clinical anaesthesia.

DISCUSSION

In this review many of the newer intravenous barbiturates have been "weighed in the balance and found wanting". Buthalitone, methitural, B.137 and B.82 were all introduced and studied in the hope of finding a compound with a more rapid recovery rate than thiopentone. In no instance has this claim been substantiated and, furthermore, none of these compounds produced as good anaesthesia as thiopentone.

Apart from its lower potency, Inactin appears to be as good a compound as thiopentone, but does not seem to possess any advantages over the standard drug.

Methohexital alone appears to offer the only advance in the field of intravenous barbiturate anaesthesia. It is much more potent that thiopentone and there seems little doubt that the claims for brevity of action will stand critical analysis. It may produce a less severe degree of hypotension than thiopentone and there is a possibility that its local irritant action is less severe. Against these advantages there appears to be a higher incidence of excitatory phenomena and respiratory upset and, while this is reduced by the pre-operative use of an opiate, it is increased by phenothiazine premedication. Apart from methohexital, it may well be that further advances in intravenous anaesthesia will come from non-barbiturate drugs.

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BERNARD JOHNSON MEMORIAL

The following letter, which appeared in the last issue of the Journal, is reprinted as a reminder to our readers:

Sir,—An appeal for funds to set up a memorial to Bernard Johnson was launched last March. It was hoped at that time to raise the sum of £6,000, which would cover the cost of a memorial plaque to be placed in the Research Laboratories of the Faculty and to endow the salary of the Faculty Adviser in Postgraduate Studies. To date approximately £3,000 has been raised, which falls some way short of the minimum required for this endowment.

An anonymous donor has most generously offered to match any further donations received before March 27, 1961, when the fund will be closed. Should any of your readers wish to subscribe, or to add to their previous donations, their contributions should be addressed to me at the Faculty of Anaesthetists, Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2.

GEOFFREY ORGANE,
Dean, Faculty of Anaesthetists,
Royal College of Surgeons.

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LACK OF CORRELATION BETWEEN ELECTROENCEPHALOGRAPHIC EFFECTS AND PLASMA CONCENTRATIONS OF THIOPENTONE*

BY

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The electroencephalograph has been proposed as a useful instrument to monitor and control the depth of anaesthesia with certain agents during surgical operations (Gibbs, Gibbs and Lennox, 1937; Wyke, 1958). An attempt was made to evaluate its application to thiopentone anaesthesia by correlating electroencephalographic (e.e.g.) patterns and plasma concentrations of thiopentone.

METHODS

Thirty-one healthy surgical patients were the subjects in this study. There were twelve males and nineteen females ranging in age from 16 to 69 years. They varied as to race, colour, stature and weight. Surgical operations were performed during the period of observation and sampling in the first seven subjects and in subject 16. In the remaining subjects, operation was delayed until the study was completed.

Each subject received atropine, 0.3 to 0.5 mg intramuscularly, about 1 hour before the period of study. No other premedication was used. The procedure began with the intravenous injection of a priming dose of 2.5 per cent thiopentone which ranged in the first twenty-two subjects between 500 mg and 1,000 mg and in the last nine subjects between 125 mg and 350 mg. The priming dose was given within 5 to 15 minutes, as rapidly as feasible without causing circulatory depression. The amount administered was that required to produce the desired e.e.g. pattern (Kiersey, Bickford, Faulconer classification, 1951). The chosen pattern was then maintained by the infusion of 0.5 per cent or 1 per cent thiopentone controlled by a servo apparatus which varied the rate of infusion according to changes in the 16 cycle per second activity of the electroencephalogram (Mazzia, Van Poznak and Artusio, 1957; Belleville, Artusio, and Bulmer, 1954). It was thus possible to maintain unconsciousness for long periods of time with relatively constant e.e.g. patterns.

In order to avoid alterations in the electrical activity of the brain due to hypoxia or hypercarbia an experienced anaesthetist assisted ventilation in each case. Oxygen was administered by face mask at high flow rates using a circle system with a carbon dioxide absorber, except where the patient was so lightly anaesthetized that he would not tolerate the mask on his face. Ventilatory adequacy was verified intermittently with a ventilation meter in several subjects. Blood gases were not measured.

At intervals of 10 to 20 minutes blood samples were obtained for determination of thiopentone content by the method of Brodie et al. (1950). Seven subjects were maintained at e.e.g. pattern 1, five at pattern 2, and ten at pattern 3, while in nine subjects the pattern was varied for different periods of time.

RESULTS

Table I summarizes the data obtained. The period of infusion of thiopentone varied from 39 to 205

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minutes. The duration was under 60 minutes in five subjects, 60 to 90 minutes in thirteen, 90 to 120 minutes in six, and over 120 minutes in the remainder.

There was no consistent correlation between e.e.g. pattern and plasma concentration of thiopentone. With pattern 1 (corresponding clinically to very light anaesthesia) plasma levels varied from 6 to 36 mg/litre; with pattern 2 (light anaesthesia) from 7 to 48 mg/litre; with pattern 3 (moderately deep anaesthesia) from 10 to 50 mg/litre; with pattern 4 (deep anaesthesia) from 28 to 42 mg/litre. In an isolated sample at pattern 5 (subject no. 7) the concentration of thiopentone was 31 mg/litre.

Examination of table I emphasizes the futility of efforts to correlate plasma concentrations and e.e.g. patterns. For instance, plasma levels ranging from 21 to 26 mg/litre were associated with an unvarying pattern 2 in subject 23 but the same range of plasma concentrations (22 to 27 mg/litre) in subject 13 coincided with e.e.g. patterns 4, 3 and 2 in turn, and a similar range (20 to 27 mg/litre) in subject 6 with a persistent and clear cut pattern 3. On the other hand, subject 16 remained at a steady pattern 2 with a much higher range of blood levels (33 to 48 mg/litre). Subjects 3 and 4 were both maintained at a constant pattern 3, yet plasma levels of thiopentone in the former ranged from 18 to 24 mg/litre and from 33 to 50 mg/litre in the latter. It is worthy of note that in subject 3, pattern 3 was attained gradually from pattern 2, whereas in subject 4 pattern 3 was reached on the rebound from an initial pattern 4.

There were many subjects maintained for prolonged periods at a constant pattern in the electroencephalogram in whom the plasma levels of drug tended to rise successively higher (nos. 1, 3, 4, 15, 16, 17, 21, 23, 24, 25, 26, 27, 29, 30). The possible significance of this finding is discussed below.

It was also impossible, except in most general terms, to correlate either the e.e.g. pattern or the blood level of thiopentone with the clinical status of the patient. For example, subjects 19, 21, 22 and 23 all moved in response to venepuncture, although the e.e.g. at the time showed pattern 3, corresponding to the Kiersey, Bickford, Faulconer classification of deep anaesthesia. It is also noteworthy that surgical operations were performed on the first seven subjects at e.e.g. pattern 3 with blood levels ranging from 11 to 50 mg/litre, while subjects 19 and 20 were clinically very lightly anaesthetized and moving despite an e.e.g. showing pattern 3 with corresponding blood levels from 14 to 21 mg/litre.

DISCUSSION

Gibbs, Gibbs and Lennox (1937) first suggested the use of the electroencephalogram as a measure of depth of anaesthesia during surgical operation. Classifications of the sequence of changes in electrical activity of the brain associated with increasing depth of anaesthesia with the volatile anaesthetic agents have been described in detail (Brodie et al., 1951; Faulconer, 1952; Possati et al., 1953). Faulconer and his colleagues at the Mayo Clinic have reported that under conditions of equilibrium there is an almost linear correlation of the alterations in e.e.g. pattern with concentrations of the anaesthetic agent in arterial blood for ether (Faulconer, 1952), and for cyclopropane (Possati et al., 1953). Concentrations of either drug in plasma corresponding to each different electroencephalographic pattern were reproducible and varied little from patient to patient. The Mayo workers also described a classification of patterns for thiopentone but did not attempt a correlation with plasma concentrations of this drug.

The results reported in this paper indicate that with thiopentone there is relatively little connection between e.e.g. patterns and plasma drug level (table I). It is true that there was a distinct tendency for the lowest plasma concentrations to be associated with the patterns of light anaesthesia and the highest with those of deep anaesthesia. Nevertheless, there was such extensive overlapping of the ranges of plasma levels corresponding to each e.e.g. pattern that, except for very high or very low values, it would be impossible to prognosticate accurately either e.e.g. pattern or clinical status for an isolated plasma level of thiopentone.

The observation was made with prolonged maintenance of a constant e.e.g. pattern and clinical depth of anaesthesia, that plasma concentrations of thiopentone tended to rise successively higher, especially after the first hour. This

Subj. No.	Sex Age	Fat Lean Musc. (kg)	Time on drug (min)	Prime dose (mg)	Total dose (g.)	E.e.g. level	Plasma drug levels (mg/l.) and time from start (min) of prime										Remarks
							B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	
1	M 46	F 95	70	750	1·4	3	13·3 (28)	23·4 (46)	27·3 (63)	18·4 (93)	15·3 (114)						Stop drug at (75). Awake at (163). Op. from (23) to (133). E.e.g. 2–3.
2	M 34	L 52	39	990	1·49	3	37·8 (8)	38·2 (25)	23·2 (47)	19·6 (67)							Stop drug at (39). Awake at (244). Op. from (9) to (32). E.e.g. 4–3.
3	F 38	F 38	78	720	2·34	3	19·0 (16)	19·3 (31)	23·5 (46)	23·4 (60)	18·6 (81)	18·3 (100)					Stop drug at (78). Awake at (181). Op. from (37) to (72). E.e.g. 2–3.
4	M 26	L 54	55	936	2·57	3	43·0 (15)	47·3 (30)	50·2 (45)	36·7 (65)	32·9 (85)						Stop drug at (55). Awake at (95). Op. from (23) to (55). E.e.g. 4–3.
5	F 58	F 77·6	75	908	2·6	3	21·8 (15)	31·5 (32)	28·6 (44)	28·2 (60)	19·5 (86)	16·6 (106)					Stop drug at (60). Awake at (144). Op. from (15) to (30).
6	F 36	F 73·5	105	944	4·53	3	19·7 (15)	24·8 (32)	27·0 (47)	25·6 (62)	23·8 (78)	22·3 (97)	19·1 (117)	13·3 (137)	10·8 (157)		Stop drug at (105). Awake at (180). Op. from (20) to (105).
7	F 48	F F	64	896	2·05	3 5	27·9 (18)	25·1 (38)	 30·9 (54)	27·9 (78)							Stop drug at (54). Awake at (173). Op. from (3) to (73).
8	M 44	F 79·3	94	590	2·8	2 3	17·1 (16)	17·9 (30)	21·1 (45)	 32·8 (90)							No operation. Discontinued because of tachycardia.
9	F 41	F 68	76	672	2·64	2	17·1 (4)	25·4 (22)	28·5 (38)	 39·8 (47)	 41·9 (62)	 37·8 (76)					No operation. No response to venepuncture.
10	F 51	F 65·8	87	696	2·54	2 3	12·7 (26)	24·7 (49)	 24·6 (58)	 20·1 (72)	 30·0 (87)						Short period of level 3 between B1 and B2.
11	F 39	F 83	69	1062	2·56	3 2	23·5 (24)	 27·7 (39)	 25·8 (54)	 24·0 (69)							E.e.g. 3–2.
12	M 54	L 70	78	948	2·83	3	32 (33)	26·9 (48)	30·6 (63)	27·6 (78)							E.e.g. 3–4–2–3. Level 2 for short time between B3 and B4. Moved once between B1 and B2.
13	F 69	F 63·7	54	460	·5+	4 3 2	27·5 (37)	 22·4 (41)	 25·5 (54)								Stop drug at (11). Apnoea at (11). Spontaneous respirations at (17). E.e.g. 2–5.
14	M 43	M	65	920	2·52	4 2	28·8 (21)	 16·7 (39)	 13·6 (56)	 11·9 (69)							E.e.g. level 5 right after priming dose. Drug stopped after B1 and no more given.

15	F 36	L 49	76	500	2·5	2	10·7 (30)	16·9 (45)	36·6 (60)	31·4 (76)							Clinically light. Move on venepunctures.
16	M 20	M 79·8	105	450	3·77	2	33·1 (60)	38·1 (75)	42·2 (90)	47·8 (105)							E.e.g. level 1–2. 60 min prime before steady level 2 achieved. Phlebectomy (spinal) during experiment.
17	F 18	M	59	375	·7±	1	15·9 (25)	16·7 (42)	18 (59)								Moved on all venepunctures.
18	M 41	M 55·6	98	500	2·0	2 1	26·9 (68)	24·8 (83)	24·9 (98)								Stormy induction hiccups. Apnoea, vomiting. E.e.g. 3–2–1. Moved on venepuncture for B1 and 3, not B2.
19	M 35	M 69·3	52	525	1·63	3	19·5 (22)	19·5 (37)	20·6 (52)								Moved on venepuncture for B1–2, not for B3.
20	F 36	F	66	825	2·23	3	29·6 (33)	34·7 (48)	21·2 (96)								Prime doses lasted 35 min. Drug stopped at (58) as e.e.g. level almost 4 (between B2–B3).
21	F 63	F 80·7	72	950	2·15	3	14·3 (42)	15·7 (57)	16·4 (72)								Small prime doses over 4 min period with e.e.g. varying between level 1 and 2. Moved on all venepunctures.
22	F 46	L 55	90	975	2·175	3 2	30·2 (23)	29·6 (38)	34·6 (53)	26·6 (75)	30·6 (90)						E.e.g. 1–2–3. Moved on venepuncture for B1 and B2, slipped into level 2 for 22 min after B3 at (75) B.P. depressed.
23	F 34	F	104	350	2·975	2	20·9 (24)	21·1 (39)	21·0 (54)	21·4 (69)	25·1 (89)	25·9 (104)					Very steady e.e.g. Moved on all venepunctures.
24	M 16	M 47·3	120	200	2·0	1	11·1 (15)	14·4 (30)	18·5 (45)	22·6 (60)	24·8 (75)	25·4 (90)	34·4 (105)	36·4 (120)			Clinically light. Moved violently on venepuncture. After observation given ether 30 ml for removal of t and a. Returned to theatre after 5 hr. Still asleep, no drug needed. Not fully awake 20 hr after prime dose.
25	M 30	M 70	113	350	1·55	1	6·9 (18)	8·5 (33)	9·27 (48)	9·25 (63)	11·41 (78)	11·59 (93)	12·48 (108)	11·21 (122)			B8 drawn 9 min after drug stopped. Talking drowsily throughout. Slight nystagmus.
26	M 48	L 53·6	165	250	1·3	2	8·8 (23)	8·5 (38)	8·9 (52)	10·4 (70)	9·8 (90)	13·8 (105)	17·3 (120)	17·5 (135)	19·7 (150)	18·7 (165)	Clinically light. E.e.g. constant. Moved on venepunctures. Occasionally responded to voice.
27	F 47	F 57·8	158	125	1·2	2	7·29 (40)	10·06 (55)	13·7 (70)	11·1 (86)	10·2 (99)	13·1 (115)	14·2 (130)	14·3 (158)			Between B3 and B4, e.e.g. approaching level 3, drip slowed. Moved on venepunctures.
28	F 49	F	175	350	1·55	1	9·5 (52)	12·5 (70)	10·7 (90)	9·9 (105)	8·6 (132)	8·4 (145)	7·3 (160)	7·5 (175)			Clinically light. Talking drowsily throughout. Moved on venepunctures.
29	F 43	F 55	170	200	1·34	1	8·5 (30)	10·5 (55)	9·3 (75)	10·7 (100)	11·3 (125)	11·0 (145)	11·9 (170)				Depressed B.P. Moving and talking throughout. Used bedpan between B6 and B7.
30	F 52	F 61·6	205	200	1·5	1	5·66 (50)	5·90 (70)	6·56 (90)	5·83 (110)	8·05 (130)	9·72 (155)	14·1 (185)	12·7 (205)			Talking, groaning, moving throughout.
31	F 48	F	163	200	1·35	1	6·5 (20)	8·6 (38)	6·4 (57)	6·8 (73)	7·5 (89)	7·9 (105)	8·2 (121)	8·1 (140)	7·2 (163)		Talking, moving throughout, adding and subtracting numbers between B7 and B8.

appears to be a form of acute tolerance to the drug, a phenomenon previously demonstrated after large initial doses of thiopentone (Brodie et al., 1951). The last nine subjects in the present series received very small initial priming doses and relatively small total doses over a long period of time. The gradually rising plasma levels in eight of the nine subjects in the face of a constant e.e.g. pattern and clinical picture could well be explained by the development of acute tolerance.

This increased tolerance could not be due to accelerated biotransformation, since the plasma levels rose progressively. Altered permeability of the blood-brain barrier, another theoretical possibility, seems unlikely for such a highly lipid soluble substance as thiopentone without a marked change in plasma pH.

It is more reasonable to implicate a true tissue adaptation. In a manner still undetermined, upon prolonged exposure to thiopentone the central nervous system develops resistance to the depressant effects of the drug. Under these circumstances no consistent correlation between plasma levels and e.e.g. patterns is possible.

Whatever the mechanism, it would appear that concentration of drug in plasma is not the sole determinant of depth of anaesthesia with thiopentone.

SUMMARY

Studies in man showed no consistent relationship between plasma concentrations of thiopentone and e.e.g. patterns. A likely explanation is the development of acute tolerance to the effects of the drug.

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THE STIMULANT EFFECT OF WAKEFULNESS ON RESPIRATION: CLINICAL ASPECTS

BY

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IN man at rest the volume of ventilation is generally believed to depend mainly on the carbon dioxide tension in the respiratory centre and its effect on intracellular pH. This belief is based on two considerations: firstly, that respiration is extremely sensitive to increases in the partial pressure of carbon dioxide (Pco_2) (Haldane and Priestley, 1905; Nielsen, 1936; Alexander and colleagues, 1955); and secondly that apnoea occurs if the Pco_2 falls below a critical threshold tension (Haldane and Priestley, 1905; Nielsen, 1936; Douglas and Haldane, 1909). However, there is uncertainty concerning the precise value of the threshold or "apnoea point" (Lindhard, 1933) and estimates ranging from 30.5 to 48 mm Hg have been published.

Hypocapnoeic apnoea was first observed in 1868 in anaesthetized animals (Pflüger, 1868) and ever since has been tacitly assumed to occur also in the unanaesthetized animal, although this assumption has remained experimentally unverified. In anaesthetized human subjects apnoea is easily induced by overventilation; the threshold Pco_2 averages 38 to 43 mm Hg with nitrous oxide and thiopentone (Fink et al., 1960) and from 33 to 37 mm Hg with halothane (Hanks, Ngai and Fink, 1961). Perhaps again partly by analogy, a respiratory threshold Pco_2 is also believed to exist in unanaesthetized man, although the evidence for this is not conclusive. Both nonoccurrence (Henderson, 1909–10; Boothby, 1912; Mills, 1946) and occurrence (Douglas and Haldane, 1909; Lindhard, 1933; Mosso, 1903; Brown, 1953) of apnoea in acute hypocapnoea have been reported in waking subjects. Unfortunately, neither group of observations is entirely reliable. The experimental subjects in some studies included the investigators themselves who may have been influenced by foreknowledge of the expected results. Unintentional breath-holding after overventilation could easily be mistaken for hypocapnoeic apnoea, the two being hardly distinguishable without the aid of electromyograms of respiratory muscles or radiographs of the larynx. On the other hand, selfconscious breathing might unwittingly result in a spuriously low incidence of apnoea. To avoid such errors respiratory studies on conscious volunteers are best confined to naïve subjects ignorant as far as possible of the objectives and methodology.

A study of this type (Fink, 1961) was recently reported on 13 healthy men, who underwent from 2 to 8 minutes of forced breathing or of mechanical overventilation (fig. 1). The end-tidal carbon dioxide tension (Pco_2) was reduced to a mean of 22 mm Hg $\pm$ 4. Nevertheless, on discontinuing hyperventilation, rhythmic spontaneous respiration immediately resumed in every experiment. Not a single instance of apnoea or of periodic breathing was observed. On the contrary, in the first minute of recovery, ventilation was usually greater than before the test. Subsequently, the minute volume fell to about two-thirds of the control minute volume, remaining relatively steady at this level for several minutes (fig. 2). During this time the frequency of respiration was about the same as the control frequency, while the end-tidal Pco_2 gradually rose toward normal. The complete absence of apnoea in these waking subjects was in notable contrast to the result of overventilation during anaesthetic sleep, where apnoea is the rule. It was concluded that waking subjects recovering from acute hypocapnoea do not develop apnoea, but continue to breathe rhythmically at approxi-

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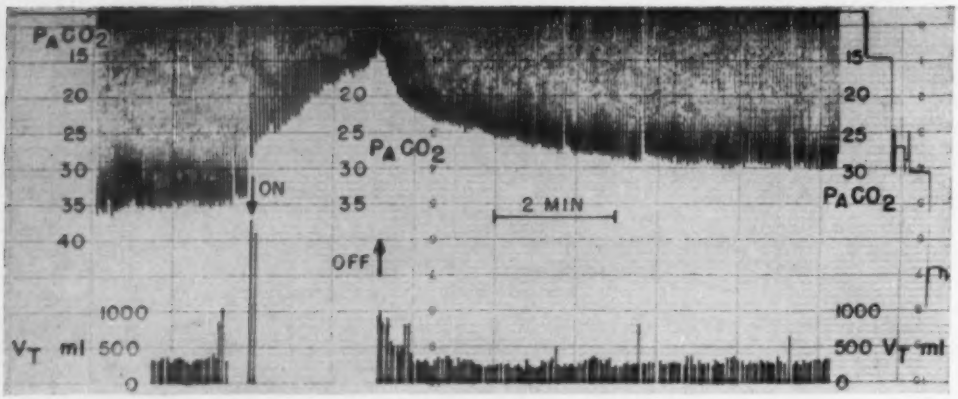

FIG. 1

Recovery from acute hypocapnoea. ON, OFF: start and end of forced breathing. P_Aco_2: carbon dioxide tension in expired air, measured by infra-red analyzer. VT: tidal volume, measured by anemometer. Forced breathing lowered the end-expiration Pco_2 to less than 15 mm Hg. After termination of the effort excessive ventilation continued during the first minute of recovery; thereafter the tidal volume was steady, approximately two-thirds of the control value. The respiratory rhythm remained regular throughout the recovery period.

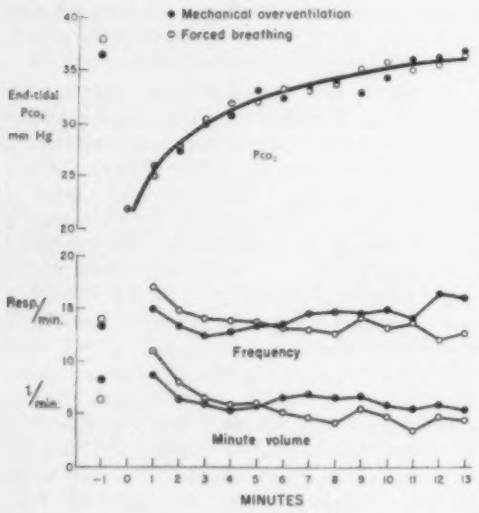

FIG. 2

Mean of observations in ten studies of forced breathing and ten studies of mechanical overventilation. A threshold tension of carbon dioxide was never reached in either group, respiration remaining rhythmic throughout in all cases. On the time axis, −1 marks the end of the control period, 0 marks the end of overventilation.

mately two-thirds of the control minute volume.

The fact that ventilation varied little during the recovery period led to the suspicion that a quite constant stimulus was at work at this time and that this stimulus must be largely independent of carbon dioxide. Furthermore, since no such stimulus is detectable during anaesthetic sleep, the unknown stimulus seemed to depend on cerebral activity associated with the state of wakefulness. Supporting evidence for the respiratory stimulating effect of wakefulness was found accidentally in two subjects who dozed off for about 20 seconds, at a time when the end-tidal Pco_2 happened to be below normal. During the brief period of sleep respiration ceased abruptly, immediately resuming when the subject was awakened by an auditory stimulus. Records of an apparently similar phenomenon have been published by Peltier (1953).

It would appear from these observations, and from others on thiopentone mentioned below, that rhythmic respiration can be maintained by wakefulness in the presence of reduced blood carbon dioxide or by increased carbon dioxide in the absence of wakefulness but not when both wakefulness and carbon dioxide are deficient.

The stimulant effect of wakefulness on respiration can be ascribed tentatively to the brain stem

reticular system, since there is evidence that both arousal and respiratory activation involve this formation. In sleeping monkeys stimulation of this system produces electroencephalogram arousal and behavioural awakening (Segundo, Arana and French, 1955). In cats, stimulation of the reticular system by carbon dioxide (Bonvallet, Huguelin and Dell, 1955) results in simultaneous electroencephalographic and respiratory activation. Clinically, somatic stimulation of lightly anaesthetized patients often elicits both augmented respiration and partial behavioural arousal, indicating that the two effects may have closely related neural pathways.

Two other clinical observations are also of interest in this connection. The recovery of spontaneous rhythmic respiration at the end of light anaesthesia with controlled overventilation often coincides with the first signs of returning wakefulness. A similar conjuncture of incipient rhythmic respiration and wakefulness occurs at the beginning of a baby's life. In both instances an apnoeic subject is on the verge both of respiration and of wakefulness and seems to cross the two thresholds almost simultaneously. Here again arousal of wakefulness appears to be associated with a strong stimulus to respiration. It must be admitted that this does not account for the patient who, although apparently awake after prolonged anaesthesia and neuromuscular blockade, fails to breathe until instructed to do so. Perhaps in some instances resumption of respiration is not so much obedience to an order as a manifestation of arousal by an auditory stimulus.

On the other hand, depression of respiration at the onset of natural sleep (Robin et al., 1958), which is usually attributed to suddenly decreased sensitivity to carbon dioxide (Fleisch, 1929), may in fact be due to depression of wakefulness and of the associated stimulus to respiration. If wakefulness stimulates carbon dioxide elimination, diminution of the wakefulness stimulus must lead to carbon dioxide retention and hence to compensatory stimulation of respiration by the retained carbon dioxide, until eventually a new steady state at a higher P_{CO_2} is attained. No altered sensitivity to carbon dioxide need be present. The reverse change, namely the stimulation of respiration observed during awakening, may indicate not so much an increased respiratory sensitivity to carbon dioxide as a return of the carbon dioxide elimination stimulus associated with wakefulness.

Depression of respiration at the onset of sleep is particularly striking when consciousness is suddenly removed by a rapidly acting hypnotic such as thiopentone. Rapid injection of an amount sufficient to abolish wakefulness (150 to 200 mg) caused a profound depression of respiration in every one of a series of twenty-three consecutive cases studied and actual apnoea in ten (table I). Recovery from the respiratory depression began within 63 seconds. One minute later, with the patient still asleep, an equal amount of thiopentone was injected. The second injection always produced much less respiratory depression than the first (fig. 3) and never produced apnoea. Care was taken to support the lower jaw and maintain an unobstructed airway throughout these observations.

It is noteworthy that the typical effect of successive injections of a barbiturate is a progressively increasing depression of respiration (Beecher and Moyer, 1941), yet in the above series the second injection paradoxically produced less depression than the first. The explanation offered is that the initial injection suppressed a strong respiratory stimulus, namely the wakefulness stimulus. Recovery of respiration occurred without return of wakefulness and was ascribable to accumulation of carbon dioxide. The subsequent injection produced relatively little depression because respiration was not subjected again to removal of the powerful wakefulness stimulus.

The wakefulness stimulus, it has been pointed out, sustains about two-thirds of the resting minute volume of ventilation, the remaining one-third presumably being due to carbon dioxide. The magnitude of the effect of carbon dioxide stimulus (Lindhard, 1933) under these circumstances is probably of the order of 1 mm Hg. This estimate is based on the fact that the resting volume of respiration is roughly doubled by a rise of 2 mm in the alveolar P_{CO_2} (Alexander et al., 1955), whence, assuming approximate linearity, a one-third decrease of ventilation would result from a fall of about 0.7 mm Hg.

Although the wakefulness stimulus appears to be fairly constant in a subject at rest, the stimulus may well be excessive in periods of anxiety or exercise, and may contribute to increased ventila-

TABLE I

Effect of thiopentone on chest pneumogram.

Patient No.	Control		Thiopentone	1st response		2nd response		Final	
	Freq.	Ampl.	mg	Freq.	Ampl.	Freq.	Ampl.	Freq.	Ampl.
1	19	10	150	0	0	14	6	12	8
2	15	10	150	15	4	16	6	16	6
3	21	10	150	20	4	16	10	16	10
4	20	10	200	15	2	24	7	20	10
5	15	10	150	15	3	13	5	13	9
6	20	10	200	15	2	22	5	23	8
7	15	10	200	15	6	19	8	17	8
8	13	10	150	13	3	15	6	14	9
9	11	10	200	0	0	18	3	15	5
10	14	10	200	0	0	15	3	15	13
11	15	10	150	0	0	14	7	13	15
12	15	10	150	12	9	12	11	12	11
13	11	10	150	13	2	12	1	12	8
14	14	10	150	10	2	14	3	14	9
15	14	10	150	14	6	16	8	17	9
16	16	10	150	0	0	14	5	14	7
17	16	10	150	16	3	13	11	13	15
18	17	10	200	0	0	21	2	20	10
19	10	10	200	0	0	15	8	19	9
20	15	10	150*	0	0	16	4	16	9
21	18	10	150	0	0	24	6	22	11
22	14	10	150	14	1	16	3	15	7
23	7	10	150*	0	0	17	5	15	6
Mean	15.0	10		14.4	2.0	16.3	6.0	15.7	9.3
S.D.					2.2		2.0		

*2nd and 3rd injections. Still awake after 1st injection.

Freq.: Lowest frequency per minute.

Ampl.: Lowest amplitude.

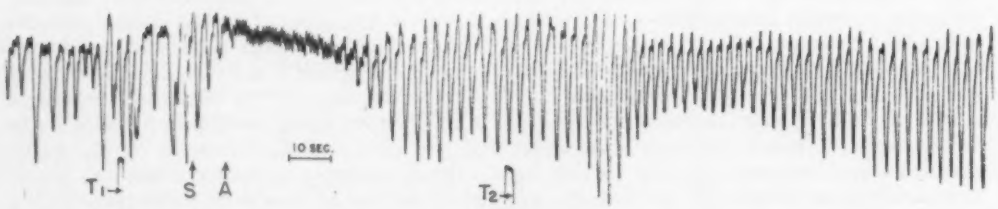

FIG. 3

Chest pneumogram during induction of sleep with thiopentone. T1, T2: intravenous injections of thiopentone 150 mg. S: subject asleep. A: onset of apnoea. The first injection resulted in suppression of wakefulness and arrest of respiration. Apnoea lasted about 10 seconds and was followed by gradual recovery of respiration but not of wakefulness. The second injection paradoxically produced much less respiratory depression than the first.

tion in the presence of reduced carbon dioxide tension such as is often observed under these circumstances (Christensen, 1931-32).

SUMMARY

Waking persons recovering from acute hypocapnoea continue to breathe rhythmically and have a respiratory minute volume approximately two-thirds of the resting value, whereas anaesthetized patients subjected to acute hypocapnoea develop apnoea. The existence is inferred of a powerful respiratory stimulus dependent on wakefulness activity of the brain. The wakefulness stimulus is apparently supplemented by carbon dioxide, the extent of the supplementary stimulus varying oppositely to the intensity of the wakefulness stimulus. Several varieties of depressed respiration and of apnoea can be explained by this mechanism.

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A MODIFIED METHOD FOR THE DETERMINATION OF HALOTHANE AND OTHER HALOGEN-CONTAINING ANAESTHETICS

BY

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DUNCAN (1959) described a method for determining halothane in tissues, body fluids and gases, based on the liberation of chloride and bromide ions by the action of an ethereal solution of lithium aluminium hydride. The reagent is somewhat troublesome to prepare and can only be kept under conditions which rigidly exclude moisture. Some workers have experienced difficulties in obtaining anhydrous ether and the method presents some fire hazard. In this note we show that lithium aluminium hydride can conveniently be replaced by finely dispersed sodium which is available in an easily handled form. Apart from the reduction stage and the destruction of the excess of reagent the procedure is identical with that described by Duncan.

REAGENTS

(1) *Dispersed sodium.* The sodium is obtained as a 25 per cent ultrasonic dispersion in petroleum jelly from Imperial Chemical Industries Limited, General Chemicals Division, Widnes, Lancashire. The material is safe to handle with reasonable precautions. The gelatinous product forms a thin skin on its surface which largely protects it from further attack by atmospheric moisture. For use, part of the surface skin is scraped away, and a suitable portion of the dispersion removed with a spatula and transferred to a thoroughly dry solvent. Any unwanted excess of sodium can be safely destroyed by transferring it in small amounts to isopropanol; it must always be kept away from water; ethanol should not be used to destroy it because the reaction is too vigorous.

(2) *Sodium suspension.* Light petroleum (b.p. 100–120°C) is thoroughly dried by contact with sodium wire. A stoppered flask partly filled with dried light petroleum is weighed. A suitable quantity of the sodium dispersion is added and the flask reweighed. The quantity added is sufficient to make a suspension equivalent to 8–10 per cent w/v of the jelly, i.e. 2–2.5 per cent w/v of sodium when diluted to volume. This suspension may be kept in the stoppered flask for several months without deterioration; it only needs mixing before use to resuspend the sodium.

(3) *Sulphuric acid 10 per cent v/v.* Concentrated sulphuric (10 ml) is added to water (90 ml).

(4) *Isopropanol.* Reagent grade.

METHOD

Halothane is extracted into light petroleum (b.p. 100–120°C) in the usual way. Sodium suspension (1 ml) is added to the petroleum extract (4 ml) and the mixture allowed to react for 10–20 minutes. Excess of the reagent is destroyed by adding isopropanol (1 ml). When effervescence has ceased, 10 per cent v/v sulphuric acid (6 ml) is added. The liberated sodium halide is extracted into the aqueous phase by gentle agitation and the mixture is centrifuged to separate the layers and provide a perfectly clear aqueous phase. Centrifugation noticeably lowers the blank values and makes the results more reproducible. The method now follows Duncan's procedure exactly.

Since the sodium suspension is virtually free from halide impurities and the amount used is not critical, it is possible to modify the above procedure to avoid the use of a weighed suspension of sodium. In this case the light petroleum extract containing halothane is placed in a tube and a piece of sodium dispersion in petroleum jelly, about the size of a split pea, is added with a micro spatula. The piece should weigh roughly 100 mg and the amount is easily judged with a little practice. The sodium quickly becomes dispersed in the petroleum and the method then proceeds as before.

RESULTS AND DISCUSSION

The results by this method closely parallel those obtained with lithium aluminium hydride. The yield of halide from halothane is slightly higher. As with the original method both bromide and chloride are liberated in non-stoichiometric but reproducible amounts. Experience with both methods has shown that the standard curve connecting optical density and weight of anaesthetic, although linear, does not pass exactly through the origin. The reason for this lies not in the reduction procedure but in the nephelometric determination of the halide, since a similar displacement of the curve is found with chloride standards.

The use of dispersed sodium for the determination of halogen in organic compounds has been described by Menville and Parker (1959). They use a coarser sodium suspension made by stirring and their method is carried out on a larger scale by titration. They claim a quantitative recovery of halide from a considerable variety of chloro and bromo compounds. Under our conditions the sodium reduction of some halogen compounds does not give the theoretical yield of halide. With halothane rather more than one equivalent of mixed halide is formed, bromide preponderating. With chloroform and trichloroethylene the yield of chloride approaches the theoretical three equivalents. We also find that 1,2,4-trichlorobenzene and pentachlorophenol yield approximately two and three equivalents respectively. With the extraction procedure designed for estimation of halothane, chloroform and trichloroethylene give somewhat lower recoveries from blood because of their lower partition ratios between light petroleum and water. However, the method could be readily adapted for use with these compounds or with newer halogenated hydrocarbons and ethers that are being developed for use as anaesthetics.

SUMMARY

Halothane and other halogen-containing anaesthetics can be conveniently estimated in body fluids and tissues by a method involving reduction with dispersed sodium and nephelometric measurement of the liberated halide.

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A NEW INTRAVENOUS ANAESTHETIC—G29505

BY

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SINCE the advent of intravenous anaesthesia a large number and variety of intravenous agents have received the attention of the anaesthetist. Recently a promising short-acting intravenous anaesthetic agent — 2-methoxy-4-allyl-phenoxy-acetic acid-N.N.-diethylamide (G29505)—has been developed. Its structure (fig. 1) is different from those of the agents hitherto used in anaesthesia.

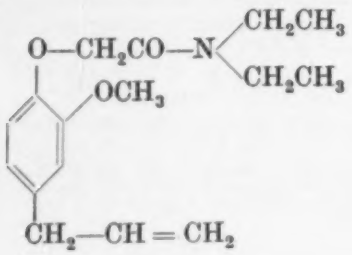

FIG. 1

The clinical use of G29505 was first reported in 1957 by Frey and Herrmann, Henschel and Just, and by Feurstein. These workers employed a 2 per cent solution in 25 per cent sodium benzoate; this solution was associated with an undesirably high incidence of venous thrombosis and phlebitis. More recently G29505 has been prepared as an emulsion in 4 per cent lecithin with 5 per cent glucose and Junod (1959) and Boureau (1959) have reported that the preparation causes less venous irritation. This emulsified form was employed in the present study. The preparation has a milky appearance and is supplied in 5 per cent strength in 10-ml ampoules. It can be injected easily through a No. 17 or larger needle.

Clinical effects.

Fifteen to 25 seconds after intravenous injection of a clinical dose of G29505 there is a sudden onset of marked hyperventilation which is followed by hypopnoea or apnoea, after which the respiration regains normal depth, although the rate is increased (fig. 2).

Successive doses also produce a brief hyperpnoea. The blood pressure shows little variation, even after doses as high as 10 mg/kg, with the patient lying flat and untilted. The pulse shows a transient marked acceleration as the patient loses consciousness. Electrocardiographic tracings were obtained in twelve patients after doses ranging from 3 to 10 mg/kg. In two patients the tracings showed transient (6 to 12 beats) flattening of the T wave shortly after the onset of sleep and in one patient a few short bursts of ventricular extrasystoles were observed just after anaesthesia started. Coincident with the loss of consciousness there is some degree of generalized muscular relaxation, relaxation of the jaw and of the vocal cords, lasting usually 30 to 120 seconds. There is also a general analgesia, the duration of which depends on, amongst other factors, the dose administered. As the effects begin to wear off phonation, purposeless limb movement, yawning and swallowing appear followed by purposeful attempts to resist surgery. Finally the eyes open and after a further period the patient becomes fully conscious and orientated. Except for a brief period immediately after loss of consciousness the tone in the neck muscles and tongue is good, so that respiratory obstruction is unlikely.

G29505 has been employed in a total of 250 patients, aged 3 to 75 years, either as the sole agent or supplemented by nitrous oxide and oxygen to provide anaesthesia for (*a*) dental extractions, and (*b*) minor casualty and outpatient surgery.

DENTAL EXTRACTIONS

In cases where only a few teeth were to be extracted G29505 was used alone; in all other cases

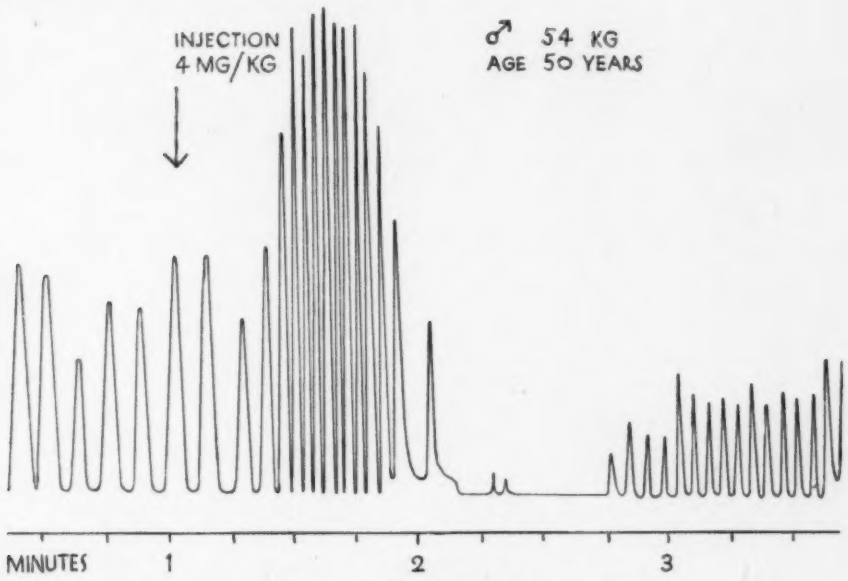

FIG. 2
G29505—spirographic tracing.

the drug was supplemented by nitrous oxide and oxygen.

G29505 alone

One hundred and seventeen patients received G29505 as the sole anaesthesia for dental extractions. The ages of the patients ranged from 3 to 49 years, the average being 16 years. (Throughout this paper patients up to and including 15 years of age are classified as "children".)

The following technique was employed: with the dental surgeon ready and the dental prop in position the drug was injected into a vein on the dorsum of the (usually right) hand. The anaesthetist then went behind the patient and supported the head and jaw throughout the extractions. The number of extractions attempted under a single dose of G29505 depended on the age of the patient and the anticipated difficulty of the extractions, whether it was necessary to reposition the prop and pack and, of course, the speed of the dental surgeon. In children up to eight extractions and in adults up to four simple extractions were attempted under a single dose of G29505. If the dose proved inadequate and the patient started to struggle a mixture of nitrous oxide and oxygen was administered to permit completion of the extractions. This was necessary in nineteen patients, either because of misjudgment of dosage or because the procedure took longer than was anticipated. These cases are analyzed together with the other nitrous oxide supplemented cases below.

Dosage. In preliminary trials dosages ranging from 2 mg/kg to 7 mg/kg were employed. It was found that the dose of G29505 had to be related to the weight of the patient, some reduction being made, however, in the very adipose patient. The dose depended also on the anticipated difficulty and duration of the extractions. The dose of G29505 used in adults is analyzed in table I. In children a proportionately larger dose per kilogram body weight was required than in adults, as will be seen in table II. Tables I and II also show the duration of the operation and of sleep. The duration of sleep was calculated from the time of going to sleep as judged by loss of the eyelash reflex (on average 20 seconds after commencement of injection) to the time when the patient was fully awake and orientated.

TABLE I

Dosage of G29505 in dental cases—adults.

G29505 dose	Number of patients	Average no. of teeth extracted	Average time to end of extractions		Average duration of sleep	
mg/kg			min	sec	min	sec
3	22	2	1	15	3	14
4	15	4	1	32	3	27
5	3	4	1	27	4	5

TABLE II

Dosage of G29505 in dental cases—children.

G29505 dose	Number of patients	Average age	Average no. of teeth extracted	Average time to end of extractions		Average duration of sleep	
mg/kg		years		min	sec	min	sec
3	22	11	3	0	58	2	50
4	23	9.6	4	1	4	3	28
5	28	7.4	5	1	19	3	57
6	4	6.2	6	1	46	3	7

Recovery. Recovery from G29505 anaesthesia was rapid. There was an obvious difference between children and adults. Frequently in children there was marked restlessness during part or the whole of the recovery period, the child aimlessly flinging his arms and legs about, moving restlessly and turning from side to side and even alternately sitting up and slumping in the chair. In adults by contrast recovery was usually quiet. A generalized tremor was noted in eight patients ranging from a slight shiver to a marked generalized trembling. This was always of short duration. Coughing frequently occurred shortly after the termination of surgery and at an average time of 1 minute 35 seconds before the eyes opened. The swallowing reflex also returned early and there was occasionally phonation or crying. Tone returned to the jaw and the patient was able to control his own head. Shortly after this the eyes opened and occasionally the patient spoke but did not yet respond to commands and showed no awareness of his surroundings or conditions. Full consciousness and orientation followed a few minutes later. The average time interval between the opening of the eyes and the return to full consciousness was 1 minute 40 seconds in adults and 1 minute 30 seconds in children. Several patients reported that in the interval before the return of full consciousness they could hear commands and instructions but were unable to comply. The patient was usually fit to proceed home accompanied within a few minutes of recovering full consciousness. The average time from the termination of extractions to going home was 9 minutes 55 seconds, the range being 3 minutes to 34 minutes.

G29505 supplemented by Nitrous Oxide

This group included nineteen patients in whom it proved impossible to do the necessary extractions under G29505 alone, and seventy patients in whom it was decided ab initio to supplement G29505 with a mixture of nitrous oxide and oxygen. Naturally the majority of the patients were adults. No premedication was administered. The average age of this series of patients was 31.8 years. In these patients after the injection of G29505, a mixture of 95 per cent nitrous oxide with 5 per cent oxygen was administered and within a short time (average 1 minute 25 seconds) the oxygen percentage was increased to 10 per cent. Usually the oxygen percentage was later increased up to 15 per cent. When a large number of teeth were to be extracted a nasopharyngeal tube was usually employed, and was introduced immediately after the induction of anaesthesia with

TABLE III

No. of teeth extracted	No. of patients	Average dose of G29505	Average time to end of extractions	Average time from end of extractions to full recovery of consciousness
		mg/kg	min sec	min sec
1–10	46	3.3	3 16	1 40
11–20	25	3.7	4 31	1 47
21–32	18	3.9	7 45	1 34

G29505 and before nitrous oxide and oxygen administration was commenced. At the end of the extractions 100 per cent oxygen was administered for a few moments before disconnecting the nosepiece.

This method provided anaesthesia free from reflex response to stimulation. The impression was formed that, using G29505, anaesthesia was easier to manage than with thiopentone and a nitrous oxide and oxygen mixture. It is possible that G29505 does not have the anti-analgesic effect which has been described following thiopentone (Clutton-Brock, 1960). This is strongly supported by the fact that despite the large numbers of teeth removed in some individuals, it was necessary to resort to volatile adjuvants in only four patients.

Table III shows the dosage of G29505 employed and the number of teeth extracted in this group of patients. In adults the commonest induction dose was 4 mg/kg. The table also shows the average time from the induction of anaesthesia to the termination of surgery and the time from the end of the extractions to full recovery of consciousness. The average time from the termination of extractions to going home (accompanied) was 11 minutes 40 seconds, the range being 3 minutes to 24 minutes.

MINOR SURGERY

G29505 alone was used to produce anaesthesia in forty patients undergoing various minor surgical operations and procedures, which are listed in table IV. It is important that sterile towels be in position and that the surgeon is ready to start before the injection is given.

In twenty-eight of the patients in this group a single dose of G29505 sufficed for the whole procedure. The dosage and the course of anaesthesia were similar to those described above for dental anaesthesia.

TABLE IV
Minor operations.

Operation or procedure	Number of patients
Incision of abscess	6
Incision of septic finger	5
Reduction of fracture	5
Manipulation	4
Removal of aural polyp	7
Removal of nail	3
Dilatation and curettage	7
Miscellaneous	3
Total	40

In the remaining twelve patients supplementary doses of G29505 were given to prolong anaesthesia. In two of these patients (removal of toenails) volatile adjuvants were required before surgery could be completed. The uneven anaesthesia produced by intermittent dosage, together with the rather slower recovery render this method of administration inadvisable. In procedures lasting more than 1 to 2 minutes it is preferable to employ G29505 for induction only and to supplement anaesthesia with nitrous oxide and oxygen, or, if necessary, with a more potent agent.

COMPLICATIONS

The following sequelae were noted in the series of 250 patients reported above.

Venous damage.

Twelve instances of thrombophlebitis were noted. (It is possible that some cases of local thrombosis occurred which were not reported.) Two patients developed slight and localized thrombosis. In eight patients there was a moderate degree of phlebitis, whilst in two patients there

was a severe thrombophlebitis with some periphlebitic lymphangitis. In one patient a small amount of G29505 had been "spilled" extravenously and a marked inflammatory reaction with oedema resulted. These incidents resolved satisfactorily with conservative treatment.

Nausea and vomiting.

Nausea, retching and vomiting occurred in a total of twenty patients. Of these, ten had received G29505 alone while the remainder had also received a mixture of nitrous oxide and oxygen. Retching and vomiting usually occurred shortly after the recovery of full consciousness and in only three cases lasted more than a few minutes.

Vertigo.

Two patients complained of dizziness after receiving G29505 alone.

Laryngeal spasm.

With the exception of one patient who developed a mild stridor during recovery, no laryngeal spasm occurred.

Amnesia.

There was no memory of the events which took place during anaesthesia. This applied even to patients in whom the dose of G29505 proved grossly inadequate and where a nasal mask had to be applied.

CONCLUSIONS

G29505 is a useful anaesthetic agent for operations or procedures of very brief duration. Supplemented by a mixture of nitrous oxide and oxygen it provides satisfactory anaesthesia for more prolonged superficial operations. It may also have distinct advantages as an induction agent before other forms of anaesthesia and its use for this purpose in obstetric anaesthesia particularly must be investigated. The use of G29505 by repeated injections does not appear to be advantageous. The risk of venous irritation has been considerably reduced in the present preparation but efforts must be made to remove entirely the irritant effect of the drug. In the field of dentistry, for multiple extractions in both adults and children, the induction of anaesthesia with G29505 and supplementation with nitrous oxide and oxygen mixtures offers distinct advantages in pleasantness for the patient, ease of management of anaesthesia, speed of recovery and relative freedom from postoperative complications. For one to four simple extractions in adults a single dose of G29505 suffices. For the removal of a few teeth in children, however, the author's preferred method remains to ask the child whether he would prefer "something to smell" or a "prick in the hand".

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ADDENDUM

Since this paper was submitted a statistical study has been carried out by Mr. R. H. Daw. This analyses the duration of sleep (i.e. time from injection to full recovery) resulting from 3, 4 and 5 mg/kg G29505 in adults. The material studied includes data from a further thirty-seven adult cases. Analysis shows a significant relationship between dose and duration of sleep.

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A REPORT ON MORTALITY AND MORBIDITY FOLLOWING 9,107 HYPOTENSIVE ANAESTHETICS*

BY

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THIS report covers the first ten years work with controlled hypotension (1950–1960) during which a series of 9,107 hypotensive anaesthetics has been administered. Of these 5,407 were administered by the author and the anaesthetic personnel of one hospital while the remaining 3,700 were administered personally in various hospitals and clinics. It would seem valuable to review the mortality and morbidity of this technique and to give for the first time an authentic analysis of a large series.

MORTALITY

There have been 9 deaths in association with 9,107 hypotensive anaesthetics (table I). This implies that death occurred at or after operation and that it was caused by the anaesthesia, the surgery or both. Of these 9 fatalities 4 followed cardiac arrest on the operation table. In 2 patients this was caused by *inadequate ventilation* and both responded to cardiac massage, but neither made a full recovery; 1 died after 13 days and the other after 28 days. Of the other 2 patients who suffered cardiac arrest 1 died from *air embolism* via the jugular veins, and the other from *adrenal insufficiency*.

The remaining 5 deaths occurred between 4 hours and 13 days after operation. In 2 instances death was due to respiratory obstruction, in one case caused by a *spontaneous pneumothorax* and in the other by *airway difficulties* in a coloured man half an hour after the operation had finished. The latter patient was resuscitated by cardiac massage but did not make a full recovery and died 4 days later. The third patient collapsed and died 20 hours after operation for block dissection of the glands of the neck for carcinoma. There is no clear indication from the records that inadequate ventilation, which can easily occur after this operation, played a decisive part in this fatal result but only that there was "cardiac collapse" in an old patient with malignant disease. The fourth fatality was caused by *severe hypoglycaemia* following an operation for osteomyelitis of the frontal bone in a diabetic tuberculous patient in whom pre-operative insulin was given in excessively large doses. Furthermore at that time the potentiation of insulin action by ganglion blocking drugs was not known.

The last fatality occurred 5 days after operation in a fat woman of 63 who was stone deaf. She underwent an extensive resection of the mandible for carcinoma and the blood pressure was not accurately controlled. The blood pressure was not accurately monitored, because this patient was operated on before the introduction of the oscillometer without which steady and accurate control is impossible. Her recovery from anaesthesia was apparently satisfactory and indeed she was discharged from the recovery ward the following day, but back in her own ward she was not co-operative and she did not appear to understand what was happening, although this aspect of her behaviour was difficult to assess because of her deafness. It is conceivable that her condition was caused by an acute mental disturbance precipitated either by operation or by hypotension or by both, and when she died 5 days later, from purulent bronchiolitis, no natural disease was found at autopsy to explain her mental condition. There is therefore some doubt as to the exact cause of this fatality.

Discussion.

From all these results it is apparent that death occurred four times because of inadequate ventilation (Case nos. 1, 2, 5, 6, in table I) in association with hypotensive drugs and surgery, and in

*Paper read at the Second Congress of the World Federation of Societies of Anaesthesiologists, Toronto, September 1960.

TABLE I
Mortality.
Total 9 in 9,107 hypotensive anaesthetics.

Case No.	Cause of death	Time of occurrence	Time of death	Operation	Age	Sex
1	Inadequate ventilation	During operation	28 days after operation	Decompression spine T.B.	F	16
2	Inadequate ventilation	During operation	13 days after operation	Facial plastic	F	42
3	Air embolism	During operation	During operation	Resection mandible, tongue and block dissection glands	M	24
4	Adrenal insufficiency	During operation	During operation	Plastic reconstruction of ear	F	40
5	Spontaneous pneumothorax	4 hours after operation	4 hours after operation	Excision mandible; block dissection glands neck	M	81
6	Acute respiratory obstruction	½ hour after operation	4 days after operation	Facial plastic	M	27
7	Cardiac collapse	20 hours after operation	20 hours after operation	Block dissection glands neck	F	63
8	Hypoglycaemic coma	During operation	4 days after operation	Osteoplastic forehead flap	M	45
9	Mental disturbance / Purulent bronchiolitis	—	5 days after operation	Excision mandible	F	63

a fifth patient (Case no. 7) this reason cannot be excluded with certainty. These results emphasize again what has been stated before—that the myocardium will not tolerate anoxia associated with hypotension. It is also vitally important to realize that residual ganglion paralysis after long-acting hypotensive drugs diminishes the capacity of the patient to withstand stresses such as respiratory obstruction or depression. When such drugs have not been given, a patient can often pull through these adverse conditions but a fatal outcome is very likely when the ganglia are paralyzed.

It is, therefore, chastening to realize that of these 9 deaths, 3 (Case nos. 1, 2, 6) were certainly avoidable by the basic principles of good anaesthesia, in particular by the maintenance of a clear airway and full oxygenation. Those associated with adrenal insufficiency and diabetes (Case nos. 4, 8) are, in the light of present knowledge of these conditions, avoided with greater certainty. It is doubtful whether the hypotensive technique was in any way responsible for the one death which occurred 20 hours after operation for block dissection of the glands of the neck (Case no. 7), whilst the patient with fatal air embolism (Case no. 3) died for reasons quite outside the control of the anaesthetist, and in association with an event which may occur at any time during an operation in the region of the great veins of the neck. The one unexplained death (Case no. 9) must be considered a likely complication of the hypotensive technique, particularly as the blood pressure was not carefully controlled but it must be remembered that this was an extensive and difficult operation in an unfit woman. This complication has not recurred in any other patient in this large series.

These figures give a mortality rate of 1 in 1,000 and it is tempting to compare this with the overall mortality rate at the Queen Victoria Hospital, East Grinstead, during the same 10-year period during which 30,950 operations were performed and 20 deaths occurred. But a detailed examination of these records shows that these deaths occurred from such a wide variety of causes that any attempt at comparison or statistics is quite worthless. Thus, for instance, this latter series includes death from coronary thrombosis 24 hours after operation and from the severe intoxication of burns 3 days after grafting, as well as deaths in the theatre from pulmonary

embolism and from an obvious anaesthetic accident. It is, therefore, of no value whatever to lump all these together in order to give a neat figure for a mortality rate, for this has no meaning. It must be pointed out, however, that whereas inadequate ventilation was responsible for so many of the fatalities with hypotension, it did not figure prominently as a cause of death in the series without hypotension.

MORBIDITY

Cerebral thrombosis.

Cerebral thrombosis occurred once in this series. A female patient, aged 25 and physically fit, developed a left-sided hemiplegia 12–16 hours after full recovery from an extensive breast operation performed under hypotension. The operation was uncomplicated in every way and the systolic blood pressure, which had not been lower than 70 mm Hg at any time during operation, quickly rose to 90–100 mm Hg on return to bed. Consciousness was soon regained and thereafter the patient appeared normal in every way, but during the early hours of the following morning paralysis was discovered. Eventually she made an almost complete recovery. The most likely explanation of this complication is found in the fact that she was nursed in the sitting position after operation and was given an injection of chlorpromazine 50 mg, 4 hours after operation and morphine 10 mg, 6 hours after that. No check was made of the blood pressure after leaving the theatre. It was not at that time appreciated that chlorpromazine often induces a very considerable fall of blood pressure when given after hypotensive drugs and that its hypotensive action is further enhanced by morphine. There is little doubt that this patient suffered a prolonged period of hypotension, probably of severe degree, induced by these drugs together with her sitting position. This would not have occurred if a postoperative record of blood pressure had been kept as is now the practice for all patients. Chlorpromazine and other drugs with a hypotensive action should be avoided during the recovery period. The long-acting hypotensive agents (such as pentolinium and hexamethonium) paralyze ganglion transmission for many hours after operation and during this time all other drugs should be used with considerable caution.

Mental sequelae.

There is no evidence that mental changes of any kind have been induced by the hypotension. Disturbances in the elderly patient are more closely related to the mental stability of the patient and to the type, nature and success of the operative procedure. One male patient, aged 46 years, became aggressive and delirious 11 days after full recovery from an operation for forehead rhinoplasty under hypotension, and the condition was diagnosed by the psychiatrist as an acute paranoid episode. After treatment for 4 days he suddenly appeared to wake up and became normal. He apologized profusely for his previous accusations and obstructiveness and was thereafter normal with a satisfactory result after replacement of the flap. He committed suicide 6 months later after a recurrence of carcinoma of the stomach, for which he had received operative treatment previously and which diagnosis was known to him.

Occasionally the elderly patient is confused for several hours after operation, but this has been observed as frequently after non-hypotensive anaesthetics. There are occasional complaints of lethargy and depression after hypotension, but again not more frequently than when hypotension is not used. Indeed there have been many opportunities for comparing hypotensive and non-hypotensive anaesthetics in the same patient at consecutive operations, and they again point out the unreliability of such symptoms in assessing the possibility of mental effects arising from this technique. Complaints occur, sometimes with hypotension and sometimes without, in such a way as to indicate that the hypotension itself bears no relationship to the symptoms. On the other hand many anaesthetists support the observation that patients who have been subjected to extensive surgery under hypotensive ganglion blocking drugs are surprisingly fit after operation. This "anti-shock" effect appears clinically to be of real value in extensive operations.

The opinion of the Recovery Ward Sister at East Grinstead after many years experience of these patients is that recovery from anaesthesia with hypotension is indistinguishable from that without.

The vomiting rate as estimated on a recent series of 300 patients, half with hypotension and half without, shows no significant difference between the two series. Sex, age, operation, premedicant and anaesthetic drugs, are but some of the many factors affecting postoperative vomiting and it is therefore impossible to obtain two series for comparison in which all the variables are constant except blood pressure. It can, however, be stated with confidence that clinically there is no very obvious difference between those who have had hypotension and those who have not.

Cardiac massage.

One cardiac arrest with full recovery after cardiac massage occurred during the writer's early experience with the technique (Enderby, 1952). This was caused by inadequate ventilation (due to the position of the patient) at the commencement of hypotension, and only bears out again what has already been stated in this respect. It is included in this section because, although the patient made a full recovery, the necessity for such drastic action must be considered a part of the morbidity rate. It is perhaps unnecessary to point out that this complication is avoidable.

There was likewise one other collapse on the table shortly after the start of a thyroidectomy operation, again caused by respiratory obstruction, in this case due to a partially kinked endotracheal tube which had not been noticed earlier. There was a sudden fall of blood pressure from 70 mm Hg to an unrecordable level (again this occurred before the introduction of the oscillometer) and at once the table was changed to a head-down position and an incision made for cardiac massage. No sooner had the skin been incised than the patient made an equally sudden recovery. Cardiac massage was not performed and the operation was completed satisfactorily. The head-up position was partially responsible for the kinking of the intratracheal tube which was relieved by the change of position. It is quite clear too that the heart had not stopped beating when resuscitation was started and the increased venous return consequent on the change of position together with an improvement in the airway avoided an otherwise certain cardiac arrest and resulted in recovery.

Both these latter complications were in the writer's personal series of 3,700 operations, and it is worth recording that they both occurred during the first 500 operations of the series. They point dramatically to the absolute necessity for perfect anaesthesia as the only sound basis for safe hypotension. This complication has not recurred in the large number of hypotensive anaesthetics performed since then.

CONCLUSIONS

What conclusions can be drawn from this large series? How safe is hypotension and how justified are anaesthetists in adding ganglion paralysis to unconsciousness? The early mistakes which were responsible for one death (respiratory depression) should no longer occur, and indeed it seems fair to observe that the skill and knowledge of the trained anaesthetist is now capable of giving adequate hypotensive operating conditions with safety. Cardiac arrest during operation has not recurred since the early days, but this must be attributed to the increased care and skill devoted to an exact knowledge of blood pressure and anaesthetic requirements. Without this care and skill the risk of cardiac arrest is considerably greater with hypotensive drugs. These figures point out that such care and skill must be carried on into the immediate postoperative period and this makes the provision of skilled nursing a necessity during recovery.

The advantages of hypotension cannot be ignored in trying to assess justification for a technique with known dangers. From these results, however, it is fair to state that many of these dangers are now clearly understood, and indeed that the study of hypotensive anaesthesia has greatly enriched knowledge as to the mechanisms leading to sudden collapse and cardiac failure. The cause of death and the circumstances leading up to it are clearly understood in 8 of these 9 deaths which have been associated with hypotensive drugs. It is clear that these causes are in large part avoidable, but whereas the skill of the anaesthetist may be capable of avoiding them, it must be remembered that others are involved in the care of these patients and the level of skill throughout the surgical and nursing team may not be adequate to cope with every eventuality. But it must also be remembered, that where knowledge exists, skill will follow,

particularly when that skill is obtained by careful and exact training.

SUMMARY

This series represents 10 years work by the staff of the Queen Victoria Hospital, East Grinstead (a total of 5,407 cases), together with a further 3,700 cases anaesthetized by the author in other hospitals and clinics.

Nine fatalities occurred in association with the 9,107 hypotensive anaesthetics. Four of these, and possibly a fifth, were caused by inadequate ventilation. Air embolism, adrenal insufficiency and diabetic hypoglycaemia caused the other fatalities. In one patient cerebral complications were possibly the result of the hypotension. During the same period there was a total of 30,950 operations at Queen Victoria Hospital, East Grinstead, and these showed an overall mortality of 20. No direct comparison is made between these figures and the hypotensive series because of the differing circumstances of death which they include, but it is significant to note that inadequate ventilation as the cause of death did not figure prominently, except in association with ganglion blocking drugs and hypotension.

Cerebral thrombosis occurred in one patient. There were no other cerebral or mental complications.

Cardiac massage successfully resuscitated one patient. Another patient collapsed at the start of operation but recovered before cardiac massage was commenced.

No significant difference was noted in the vomiting rate when compared with a similar series of non-hypotensive anaesthetics.

No other complications were reported which were attributable to the hypotension.

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SOME SUGGESTIONS FOR THE NEURAL BASIS OF THE ANAESTHETIC STATE*

BY

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THE purpose of this paper is to put forward some ideas about the neural basis of the anaesthetic state and to see what support, if any, can be adduced for these by a survey of present knowledge of the neural mechanisms of consciousness and how these can be altered by psychotropic drugs.

THE NATURE OF CONSCIOUSNESS

Consciousness still defies precise definition although knowledge of some of the neural processes involved has widened considerably in recent years.

It is known, for example, that the watchful, alert, or attentive state is dependent on the ability of the ascending reticular system to induce electroencephalographic and behavioural arousal in the cerebral cortex. Without this "arousal reaction" messages arriving at the sensory receiving areas of the cortex cannot undergo the complex integrative processes necessary for their elaboration into consciousness (Magoun, 1958a).

These integrative processes appear to be of at least two distinct kinds. The first concerns perception—that is to say recognition of the identity of an incoming signal. The second and more complex is the endowment of this perception with a conceptual value (Herrick, 1949; Herrick, 1956), which involves memory, association, emotion, and learning.

It can be argued that ability to perceive is itself an adequate definition of consciousness. To a certain extent this is true, for otherwise a newborn babe could not be said to be conscious, since it has not had time to develop conceptual values. To do this requires experience and memory. It may be that this is why it is not thought necessary to anaesthetize an infant for the operation of circumcision whilst laporotomies can be performed at this age under d-tubocurarine and oxygen.

Only as growth proceeds does the power of endowing perceptions with conceptual values develop. These find expression in behavioural and emotional responses which it is the task of the anaesthetist to overcome or modify. Consequently it is of interest to see how far it is possible to define the neuronal processes involved and the extent to which they are susceptible to different classes of sedative drugs.

THE NEURONAL MECHANISMS OF CONSCIOUSNESS

It seems probable that perception is the consequence of the interaction of neuronal processes which a peripheral stimulus sets up in the ascending reticular activating system and at the sensory cortex. This manifests itself by alertness, the focusing of attention and desynchronization of electroencephalographic rhythms (Lindsley, 1957).

However, in order for the perception to acquire conceptual value the participation of the temporal lobe and the rhinencephalon appears necessary.

Wilder Penfield (Penfield, 1958) has drawn attention to the importance of the temporal lobe in the exercise of the function of memory. He has suggested that it should be distinguished from the sensory and motor cortex by receiving the name of "interpretive" cortex. The temporal lobe is necessary for the recall of past experience and through the medium of this structure signals arriving at the sensory cortex are able to reactivate old patterns of neural activity set up by similar signals in the past. Clearly this supplies the basis for creation of conceptual value. The underlying rhinencephalon (the old brain or the visceral brain) has also received increasing attention in recent years for the part it could play in determin-

* Based on a paper read before the 2nd World Congress of Anaesthesiologists, held at Toronto, September 1960.

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ing behavioural responses which are also closely related to the conceptual component of consciousness.

The rhinencephalon is intimately connected with, and under the influence of, the ascending reticular activating system. Connections have been traced from the intralaminar nuclei of the thalamus through the septum and dorsal fornix to the hippocampus, whilst a return pathway has been described which leads back to the midbrain reticular system by way of the external capsule, anterior commissure and the stria medullaris (Adey, 1955; Adey, Merrillees and Sunderland, 1956). This re-entrant circuit furnishes a pathway for the initiation of the autonomic and endocrine disturbances which accompany conditions of predicament and emotional stress. The hippocampus receives fibres from all the surrounding parts of the brain—visual, auditory, olfactory, visceral, parietal and temporal (Papez, 1957). It thus provides a common field for a variety of reactions expressing emotional moods as well as a place for the integration of cortical processes from several different sources into the conceptual component of consciousness.

Animal experimentation also supports the view that this part of the brain is responsible for behavioural response to environmental situations (Green, 1957). Everything points to the limbic system as a key structure in the formation of the conceptual processes of consciousness which arise through the interaction of the ascending reticular activating system, the neocortex, the temporal lobe and limbic system. The site of the final integrative processes is not known but Penfield's suggestion is that they occur in a subcortical "centrencephalic" system which he defines as "coordinating and organizing fibre and cell connections in the higher brain stem" (Penfield, 1957).

Expressed in a simplified form consciousness may be said to depend on:

(*a*) The integrity of a nonspecific subcortical system known as the ascending reticular activating system. This extra-lemniscal sensory pathway seems to be kept in activity by afferent stimuli from all modalities of sensation much of which reaches it by means of collaterals from the lemniscal pathways. These stimuli give rise to diffuse neuronal activity which results in alertness and wakefulness and puts the cerebral cortex in a position to integrate the specific sensory messages, which continue to pass direct to the cortex.

(*b*) Two cortical integrative mechanisms subserving perception and conception both of which must converge in a central subcortical "centrencephalic" system before consciousness can be said to exist.

SOME PHARMACOLOGICAL CONSIDERATIONS

The susceptibility of these neural processes to certain types of drugs makes it possible to modify or abolish consciousness without simultaneous suppression of activity in the remainder of the central nervous system. For example, there have been several convincing demonstrations that small amounts of anaesthetic agents bring neuronal activity in the ascending reticular activating system to a standstill and render it impervious to afferent stimuli. The arousal reaction (behavioural or electroencephalic) no longer can be produced, although other parts of the brain remain active since it has been shown that signals continue to be transmitted up the lemniscal pathways to the sensory cortex, where the responses they evoke often show increased amplitude (Magoun, 1958b).

However, loss of consciousness can also result from depression of the mechanisms which it has been suggested are responsible for the perceptive and conceptual components of consciousness, by centrally acting drugs, which so far as is known, do not have any direct depressant action on the neurones which comprise the ascending reticular system.

Thus, it is possible to induce a light plane of anaesthesia by the simultaneous intravenous injection of a powerful tranquillizing drug (chlorpromazine) and an opiate (morphine or pethidine) although neither of these given separately and in similar dosage exhibits this property.

It is widely agreed that opiates reduce sensation of pain; that is to say, they reduce intensity of perceptive processes. Their lack of effectiveness in the presence of pain complicated by exaggerated conceptual processes and behavioural responses is well known, for example in the distressed primagravida in active labour. Whilst precise knowledge about the exact place and manner of the action of opiates is lacking, there is very suggestive evidence of an action in the region of the corona radiata (Wikler, 1950; Seevers, 1954). A depression at this site could inter-

rupt integrative neuronal activity between the cortex and the subcortical systems which appear to be concerned in subserving the perceptive component of consciousness.

The tranquillizing drugs as typified by chlorpromazine have no apparent depressant action on perceptive processes but have a remarkable ability to depress mechanisms responsible for formation of conceptual processes. This type of sedation has been variously described as "ataraxia", "antiphobia" and "tranquillization" but on analysis this turns out to be a loss or modification of the behavioural response to different environmental situations, especially those that are "stressful" (using that term in its widest sense). There is no interference with perception but the emotions which perception arouses are reduced or absent; or, put in another way, there is interference with the elaboration of conceptual processes. Studies of the central actions of these drugs appear to lend support to this hypothesis.

In spite of many claims that the more powerful tranquillizers abolish the "arousal reaction" by a direct repression of the ascending reticular activating system these effects have not been confirmed. Bradley has shown that chlorpromazine (and other tranquillizers of similar potency) reduce neuronal activity in the ascending reticular system by means of a depressant action on afferent input at the point where collaterals from the lemniscal pathways enter the reticular system (Bradley, 1958–59; Bradley and Key, 1959). The neocortical arousal response is little altered but there seems to be a definite depression of the hippocampal arousal reaction (Vogt, 1958). This differs from the neocortical arousal in that the characteristic alterations of rhythm which accompany the change from the inattentive sleepy state to one of wakefulness and alertness are the opposite of those which take place in the neocortex (Magoun, 1958c; Adey, 1955).

The opiates and the tranquillizers can therefore be said to have a selective depressant action on two of the neuronal processes necessary for full consciousness; one responsible for pain perception and the other for the accompanying conceptual processes. Their combined action is sufficient to abolish consciousness without any simultaneous direct action on the ascending reticular activating system.

HIBERNATION AND ATARALGESIA

This furnishes us with a method of inducing anaesthesia at a small cost in terms of depression of cellular activity elsewhere in the body, such as must occur to some extent when more powerful general protoplasmic poisons are used for this purpose.

The state of "hibernation" is nothing more than anaesthesia of a light plane produced by intravenous injection of opiates and tranquillizers. Once induced it is possible to allow surgery to begin, sometimes without further medication, or supplemented by a small dose of thiopentone, or nitrous oxide given with a high percentage of oxygen.

The interesting condition known as "ataralgesia" can be explained in terms of the actions of the drugs used on perception and conception. To induce this state large doses of opiates (much larger than those used in hibernation) are combined with one of the less potent tranquillizing agents. The effect of this combination is to induce a state where consciousness is still retained but pain sensation abolished to the extent that in many instances operations can be performed without additional anaesthetic agents. Perception is effectively dulled by the rather large doses of pethidine used (200–300 mg) but conceptual mechanisms are not depressed to the point where consciousness is lost. If an attempt were made to carry out this method using a powerful agent like chlorpromazine together with these large amounts of opiates a deep state of anaesthesia would ensue sufficient for surgery but recovery would be very prolonged. This is, in effect, what happened when chlorpromazine was first introduced into anaesthesia; the heavy opiate premedication (papaveretum and hyoscine) which preceded injection of the "cocktail" produced deep unconsciousness ("anaesthesia without anaesthetics!") and a much delayed recovery. This gave the method a bad name amongst those surgeons who like a rapid postoperative recovery. However, by keeping down the amount of opiates (never in excess of 100 mg pethidine) a state of unconsciousness or light anaesthesia can be obtained which only needs the addition of minimal quantities of stronger agents. After operation the return of consciousness is rapid and side effects are minimal.

LIGHT ANAESTHESIA AND MOTOR RESPONSES

"Hibernation" then is nothing more than a very light plane of anaesthesia produced by abolishing perceptive and conceptual processes. There are, however, several other ways of inducing a light plane of anaesthesia. Whatever method is chosen, it must be appreciated that this does not guarantee that the patient will not respond by limb movements to surgical stimulation. This response does not necessarily indicate a return of consciousness. Adrian and Moruzzi (1939) showed some years ago that these movements occurred in animals anaesthetized by various agents and that they depended on the rate of neuronal discharge evoked in the pyramidal tracts by the arrival of signals at the sensory cortex. This discharge was continuous in all but the deepest planes but when it reached a certain intensity it gave rise to movements of the limbs.

This motor response which is involuntary can, in clinical practice, be prevented by increase of the overall anaesthetic concentration (undesirable except in short procedures), by intravenous injection of opiates, or by paralyzing the patient with a muscle relaxant which ensures an unresponsive patient, albeit lightly anaesthetized.

This last practice is not without its drawbacks. From time to time there are reports of patients becoming conscious during anaesthesia and finding themselves immobilized or paralyzed, a situation which is unpleasant to contemplate. However, it is doubtful whether consciousness is complete in its fullest sense. Powers of perception may well be present but the effect of the drugs (usually nitrous oxide and a barbiturate) seems sufficient to prevent the elaboration of conceptual values for these circumstances, so that the full emotional response which such an experience would induce in a person not under the influence of any sedatives does not occur. It is a constant impression that these patients do not express keen resentment or horror and that their recollections appear detached and free from rancour.

SUMMARY

Consciousness could be the consequence of the interaction of two different neural mechanisms, one responsible for perception and the other for conception. This hypothesis is discussed in the light of recent neurophysiological research into the neural basis of consciousness.

Certain drugs used for sedation and in anaesthesia appear to have a selective action on the neural mechanisms underlying perception and conception whilst their combined actions abolish consciousness and produce a light plane of anaesthesia. Effective anaesthesia does not demand overall depression of central nervous activity. The specific sensory and motor mechanisms are little affected in the lighter planes of anaesthesia.

These considerations offer an explanation for the states known as artificial hibernation, ataralgesia and for the popularity of anaesthetic techniques which depend on the maintenance of a light plane of anaesthesia whilst ensuring immobility of the patient by means of muscle relaxants or small intravenous doses of analgesics.

Further thought about the neuronal mechanisms of consciousness and the action of psychotropic drugs may help to remove some of the empiricism in which our specialty has been shrouded ever since the day when Oliver Wendell Holmes coined the word "anaesthesia".

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BOOK REVIEW

Measurement of Subjective Responses. By Henry K. Beecher. Published by the Oxford University Press, New York (1959). Pp. 494. Price 102*s*.

This is a book of absorbing interest and represents the collected work of the author together with a critical assessment of the work of others and it has resulted from many years of study and thought on this subject. Professor Beecher's specific interest in the subject of pain appears to date from his war experience and thus extends back over nearly twenty years. During this time he has formulated principles based on a vast amount of careful and meticulously controlled observation particularly directed towards the investigation of the subjective aspect of pain. This is exemplified by his studies of "placebo reactors" of the "psychic" component of the pain experience and its relation to the significance of the pain to the individual. The book, however, collects together not only these studies but also a great deal of information concerning the techniques which may be used for their objective study and their evaluation.

The first part of the book is concerned with these preliminary principles and includes sections on statistical planning, the reaction factor of the pain response and on pain thresholds. To be facetious for a moment, it is surprising to find in this section "Constancy" and "Purity" as main headings. Part two deals with studies in which these techniques have been applied and compares analgesia with sedation. There is a consideration of the euphoric and dysphoric components of drug activity and experiments are described which, interestingly enough, attempt to "quantify" the action of drugs on anxiety and hunger. There is even an examination of the drugs which have been claimed to be useful to control postoperative nausea and vomiting and pruritus, and a very original chapter on "experimental and pathological cough in man", in which are examined various antitussive agents and their value assessed.

Anaesthetists who received their training before the war will recall their gratitude to Professor Beecher for his classical collection of data published as *The Physiology of Anaesthesia*, and it seems that in this book he has produced a volume likely to be a work of reference and study for a long time to come. Its scope is demonstrated by a bibliography containing 1,063 references. Its value too arises from the fact that it is a study concerning man—animal work is not his interest. It is therefore an example of the valuable contribution that can be made to pharmacology by those who have the opportunity to study the effects of the basic principles of their science applied to homo sapiens and it is an encouragement to the applied pharmacologist not to lower the objective and scientific standards which he would apply to work on animals.

Despite a certain repetitiveness which will be found irksome to some, the book is readable and very pleasantly produced.

Cecil Gray

CORRESPONDENCE

DRUG CONSUMPTION DURING ANAESTHESIA

Sir,—I have read with interest an article in your September issue (*Brit. J. Anaesth.*, **32**, 415) on the above subject. It seems to me that the results described can be explained in a quite different way from that envisaged by the author.

Dr. Keéri-Szanto claims that "translocation" can be distinguished from "transformation" by the fact that the former must follow an exponential law of decrease while the latter should be linear with time. But, as the object of his technique is to hold the plasma thiopentone level substantially constant, when on his own showing the fat depots are not even approaching saturation after several hours, the deviation from linearity to be expected in "translocation" must be very small. Even after 300 minutes of anaesthesia, if the depots were one-third saturated, a falling off from linearity of only some 10 per cent might be expected, and this can hardly be excluded by the figures quoted.

The results have been fitted to a curve by a digital computer, but the condition of zero dose at zero anaesthesia time has been imposed. It is not clear why this should have been done, as a more usual view is that an induction dose is required at the start of an anaesthetic to provide a certain base line level of anaesthesia. If the straight portion of the curve in figure 3 is extrapolated backwards to zero anaesthesia time a dose of 300 mg of thiopentone per sq.m body surface is arrived at; this could well correspond to an induction dose.

Is it not possible that, rather than an obscure exponential function requiring a mathematical tour de force for its elucidation, a simple clinical explanation is responsible for the relatively low dose up to 25 minutes? The average stimulus is much less over this time, which will be partly spent in preparing and towelling up the patient and therefore the dose required will tend to be lower. It can hardly be claimed that this effect will be averaged out over the series because it will to some extent be common to all cases. A similar argument may be used against the curves in figure 1. Here again the curves have been fitted to pass through the origin without any obvious justification. The apparent tendency for the shorter cases to require a little less anaesthetic than might have been predicted from an inspection of the straight line fitted to the longer anaesthetics might well be attributable to any of three possible causes, namely:

(1) A tendency to use for induction in very short cases a small dose of thiopentone rapidly injected, which would not even cause sleep if it were injected slowly enough to equilibrate with the aqueous phase.

(2) A tendency to use less thiopentone while the initial dose of d-tubocurarine is still exerting its maximum effect.

(3) A tendency to use for very short cases small induction doses of thiopentone might well be attributable to a general tendency for shorter operations to be less surgically stimulating.

Dr. Keéri-Szanto shows in figure 4 a good linear correlation between the rate of drug loss and plasma level, a result which is perhaps more typical of "translocation" when the recipient depot is not significantly saturated, than it is of enzymatic transformation. If any of his individual results might be expected to show a falling off in rate due to accumulation in the fat depot, it would be in his case no. 100 which lasted for 7 hours 45 minutes; the fact that it did not do so might mean that fat depots are more capacious than previously supposed. It seems to be unwise to read too much into an interpretation of this one case.

If the "loading dose" to charge the aqueous reservoirs (including probably some protein binding) is 300 mg/sq.m body surface it follows that the steady rate of loss, 105 mg/sq.m/hr is about 35 per cent per hour. Supposing, for the sake of discussion, that half of this is removed by the liver cells and transformed, and the other half passes in to the fat depots whose capacity for thiopentone (adopting for the moment Dr. Keéri-Szanto's hypothetical figures) is 4½ times that of the aqueous phase, then at the end of 5 hours anaesthesia time an amount equivalent to 87½ per cent of the loading dose will have entered the lipid phase which will be thereby approximately 19 per cent saturated. The small

deviation from linearity in this process could not be detected in figure 3.

Can it fairly be concluded, therefore, from the results presented that "beyond the first hour more than 90 per cent is transformed"? I think not.

S. J. WEBB
Barnet General Hospital, England

Sir,—It is always a pleasure for the author to learn that his paper has been found stimulating enough to elicit as long a reflection as Dr. Webb's.

Taking his points in a somewhat arbitrary order, it does not require any special justification to make a curve pass through the origin of a chosen system of co-ordinates—the opposite does. If in figure 3 of my article the straight line observed past 75 minutes would have been extrapolated to $t=0$, this would have yielded a simpler equation $Y=At+B$ .....(1)

This equation would have provided a poor fit for the first 50 minutes and it would have implied that the equilibration of the "loading charge" (B) is instantaneous. This is manifestly false; therefore an exponential correction factor has been added to account for the period during which the rapidly mixing space equilibrated *with a single compartment*:

$$Y=At+B-Be^{-kt} \quad \text{.....(2)}$$

or, written in a shorter form:

$$Y=At+B(1-e^{-kt}) \quad \text{.....(3)}$$

This equation did account for the period of equilibration and it did pass through the origin—as any curve must, which purports to describe drug requirements during the entire course of anaesthesia. In the process it also provided an excellent fit to the experimental points. The thing I liked most about it was its very simplicity. If Dr. Webb calls this an obscure exponential function he ought to see the six-component simultaneous differential equation suggested by Price and co-workers (1960) for the solution of much the same problem.

As for the mathematical tour de force in solving the equation, the numerical value of the constants A, B and k can be determined with an accuracy to two significant figures in less than five minutes by a graphical method. To prove, however, that this is the best-fitting equation is something else again. Since it involves essentially a trial-and-error method, the computer's assistance was welcome indeed.

Equation (3) accounts for better than 99 per cent of the observed variability of our data. If there were a tissue compartment exerting a significant effect on drug requirements that would equilibrate or would approach equilibrium with the rapidly mixing space later than the initial period of equilibration, but still during the period of observation, instead of (3) one would have to apply (with apologies to Dr. Webb) an equation with two exponential terms:

$$Y=At+B'(1-e^{-k't})+B''(1-e^{-k''t}) \quad \text{.....(4)}$$

in order to fit the experimental points properly. The fact that this has not been necessary because an equation no more complex than (3) will account for 99 per cent of the variability is in my opinion a strong proof against the theory that such a second drug compartment (as proposed by Brodie et al., 1950, 1952, and Mark et al., 1956, cf. references in original article) significantly influences drug requirements during surgical anaesthesia. It will not prove, however—and in this I must stand corrected—that there is not included in the constant A some equilibration so slow, with a drug space so large, that its divergence from linearity escapes detection by this means of analysis. The possibility that thiopentone continues to disappear into the fat depots *after* surgery has been specifically mentioned in the article. Its importance or lack of it is brought out in much greater detail by Price (1960). I would instead rest my case rather on observations made since this article was prepared. Time/dose curves were determined, in the same manner as described for thiopentone, for pethidine and for oxymorphone (Keéri-Szanto, 1961). Neither of these drugs is supposed to accumulate in the fat depots, yet their time/dose curves closely coincide with the thiopentone curve both as far as the size of k and the B/A ratio are concerned. It would follow that drug requirements are determined by the same factors in all three instances and therefore either thiopentone requirements are not influenced by the fat depots, or the requirements of the two other drugs are influenced by the fat depots too. To me the first alternative seems more convincing.

Concerning Dr. Webb's objections against drawing curves through the mean values in

figure 1, these curves should not imply anything more than the fact that the experimental points are not incompatible with such a construction. The numerical values were not given and there is no conclusion drawn from them in the article. Since each case contributed only one point to the data and since the anaesthetics were performed by a large number of anaesthetists with great differences in skill and experience, the data summarized in this illustration—and this is emphasized in the text—were used only to establish that there is room for legitimate doubt about the positive correlation between adipose mass and thiopentone requirements during clinical anaesthesia.

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BOOK REVIEWS

Hypothermia in Surgical Practice. By K. E. Cooper and D. N. Ross (1960). Published by Cassell and Co. Ltd., London. Pp. xl+116. Price 18*s.* 6*d.*

In addition to the main authors, chapters are written by an anaesthetist (Dr. B. A. Sellick), a neurosurgeon (Mr. L. S. Walsh), and Dr. V. Wynn, Senior Lecturer in Surgery at St. Mary's Hospital.

In the preface of this book, an attempt is made to clear up the confused terminology which has gradually crept into the literature on hypothermia. Mild hypothermia is defined as reductions in temperature to 31–35°C (88–95°F) and deep hypothermia as under 25°C (77°F). The indiscriminate use of such terms as "deep freeze", "cold narcosis", "refrigeration anaesthesia" and "artificial hibernation" is rightly deprecated by the authors.

The opening chapter on physiological considerations is the longest in the book and in 25 pages Drs. Cooper and Sellick have presented a concise summary of the essential information without delving too much into the realms of speculation. The section on measurement of temperature and factors determining the cooling rate is particularly valuable, but it is regretted that they do not offer advice as to the relative merits of the many temperature recording devices at present available. While they review the cardiovascular effects of hypothermia in detail one would have welcomed an authoritative review of the mass of published work on the various means adopted to prevent ventricular fibrillation and an appraisal of their efficacy.

The pharmacology of drugs used in hypothermic techniques is dismissed in a mere 5½ pages and this section is somewhat disappointing. Particularly notable omissions are a lack of criticism of Orton's view that halothane is of value as a "metabolic depressant to facilitate open heart surgery at normal body temperatures" and recent work on the effect of temperature on the action of muscle relaxants.

The metabolic problems in hypothermia are dealt with in a masterly manner by Dr. Wynn who ends his chapter with a well timed warning of the dangers of citrate intoxication.

From the technical point of view, surface cooling and rewarming, blood stream cooling and hypothermia with an assisted circulation are discussed simply and clearly and illustrated in some detail. While those are three of the most valuable chapters in the book, it is doubtful if they are sufficiently comprehensive to enable a reader to undertake any of the procedures described. There are many who will disagree with the anaesthetic technique described for surface cooling, but while it is not claimed to be the only or even the best method, a few words on alternatives would have been welcome. As an example, it is not clear why ether is given for such a long time or why nitrous oxide is discontinued at 32° C.

In chapter seven, Mr. Walsh gives us a very

balanced account of the value of hypothermia in neurosurgery. He also deals with its use in severe cerebral lesions but, apart from stating that it "is a useful aid in the management of these patients" he does not give us an opinion as to what patients one should treat by this means or what constitutes a hopeless prognosis.

Lest one thinks that our knowledge of hypothermia is now complete, we have thought-provoking chapters on "cavity and miscellaneous cooling methods" and "deep hypothermia". A notable error in the latter (p. 91) is induction of anaesthesia with "sodium ethyl thiobarbiturate (Pentothal Sodium)". Unintentional hypothermia is also dealt with and in this chapter there is much useful advice for those who have to resuscitate cases who have undergone long exposure to cold. Hypothermic myxoedematous coma is also discussed and it is regretted that the dose of 1-tri-iodothyroxine is not given. One would also have expected hypothermia of pituitary origin to have been included in this section.

There are other therapeutic uses of hypothermia which one would like to have seen discussed in this book, such as, for example, for thyrotoxicosis, following cardiac arrest and for hyperpyrexia of toxic or unknown aetiology. One wonders whether in 98 pages of text any authors could do justice to such a vast subject as hypothermia and this raises the question as to the ultimate value of this book. It is not intended as a comprehensive review for those concerned with the everyday use of hypothermic techniques, but will be of great value as an introduction to the subject or for those requiring sufficient knowledge of the subject for examination purposes. The bibliography is very good, the writing is most concise and clear and, with the one exception mentioned above, the reviewer was unable to detect any grammatical or textual errors.

John W. Dundee

The Pharmacology of Anaesthetic Drugs (4th edition). By John Adriani, M.D. Published by Charles C. Thomas, Springfield, Illinois; and in the British Commonwealth by Blackwell Scientific Publications Ltd., Oxford. Price 88*s*.

This fourth edition of what is undoubtedly Dr. Adriani's most popular work reflects the increase in scope of its subject over the last few years. The third printing of the third edition appeared in 1956 and this present volume has been completely revised. The writer has a copy of the third printing of the second edition before him. This was published in 1946 and extended to 86 pages. This is to be compared with the 230 pages in this, the 1960 edition.

Here will be found data on practically every drug directly associated with anaesthesia but not necessarily on every drug that the anaesthetist may be called upon to use. There is, however, a whole section on "non-anaesthetic drugs used in conjunction with anaesthesia". This section includes excellent considerations of the pharmacological methods of modifying muscle tone, of the chemistry and pharmacology of the individual drugs used for this purpose and of those used as antidotes, as well as full data on anticholinergic drugs, sympatheticomimetic agents and analeptics. A further section treats of the inorganic gases associated with anaesthesia—namely oxygen, carbon dioxide, helium, nitrogen and lastly xenon. This section is preceded by definitions of the gas laws and physical terms. It is notable that there is no specific consideration of drugs used to lower blood pressure, of the cardiac glycosides or—and this is a notable omission—of the effect of the various important electrolytes, other than Mg^{++} and Br'.

The data is presented in the pictorial and dogmatic manner characteristic of this work. Towards the end of the book there is a section in which important references are listed for each chapter. This may be of assistance to those who will tend to use the book as one for reference. One may wonder how far this type of presentation and summary of pharmacological data is in line with modern teaching, which increasingly emphasizes principles; but this edition does show some movement in that direction by its consideration of such matters as the distribution and elimination of drugs and their detoxification, "the possible sites of action of drugs on the motor system", the mechanisms of neuromuscular transmission and block, the "pharmacological behaviour of cholinergic post-ganglionic autonomic fibres" and so forth.

The reviewer has noted certain errors but considers that such are bound to occur in a work which encompasses such a wide field and includes

such an enormous volume of data. On page 113 the wrong chemical name is given for carbocaine although this is clearly a misprint—pipercolic being written for pipecolic. Occasionally one comes across information which might be misleading; for example, on page 129, it is stated that metabolism is decreased due to "muscle activity" where obviously "lack of muscle activity" is meant. A charming misprint occurs on page 170 where the use of hexamethonium in 1950 is attributed to Davison and Elderly.

Finally the book has extended its field beyond the purely pharmacological by a whole section, some 23 pages in length, on "some clinical considerations" which include pre-anaesthetic medication, disturbances in oxygen and carbon dioxide transport, the effects of hypoxia, alterations in pulmonary physiology during general anaesthesia (this is up-to-date and admirably done), respiratory acidosis and its effects, the electroencephalogram in anaesthesia, hypotension and hypothermia.

In summary, then, this is a great improvement on previous editions and a mine of information if you like your data presented in this manner.

Cecil Gray

Nitrous Oxide in Dentistry: its Danger and Alternatives. By J. G. Bourne, M.A., D.M. (Cantab), F.F.A.R.C.S. Published by Lloyd-Luke (Medical Books) Ltd., London (1960). Pp. 181; illustrated; tables 6. Price 30s.

Largely as the result of sound teaching and of the N.H.S., the standard of general anaesthesia throughout this country is acknowledged as high. There still seems, however, much to be done to improve the conditions under which anaesthesia is administered to dental patients particularly in domiciliary practice and a deal of research and political activity by various interested bodies is at present being directed towards this goal. Dr. Bourne has undoubtedly made a very considerable contribution to this end by the campaign which he has carried out over the last few years designed to direct attention of anaesthetists and dental surgeons to this problem. His crusade has been pursued with zeal and energy and its primary purpose has been to demonstrate the very real danger which results from the deliberate exploitation of hypoxia or asphyxia to supplement nitrous oxide anaesthesia. This book represents the culmination and full blossoming of a great deal of thought, some little investigation and considerable effort which the author has directed to his mission.

After a Historical Survey, the first seven chapters present convincing evidence that all is not well in this particular branch of anaesthesia. From a questionnaire sent to a wide and representative selection of dental surgeons, from reports culled from the daily press of misadventure and from personal observations, an impressive case is built up against the most commonly used technique of dental anaesthesia—nitrous oxide and "minimal" oxygen. One may quibble and question details in this case as presented. It seems at least unlikely that "the main cause of anoxia is fainting", but there will be few who will deny the conclusion that hypoxia is common under these conditions and is to be deplored. There will be some who will doubt the justification of the conclusion of Chapter 7 on the "Potency of Nitrous Oxide" that "Nitrous oxide without supplement or relaxant is too weak for ambulatory work." This seems too sweeping and requires qualification. For example, the techniques of "amnalgesia", which have been described, in the hands of many are perfectly satisfactory for suitable cases.

Following this indictment the various possible supplements to and substitutes for nitrous oxide are reviewed. It becomes clear that the author is convinced that the technique which he described some years ago in which cyclopropane, oxygen and nitrogen are inhaled from a closed inhaler with valves, is the one which he feels provides the best solution to the problem of dental anaesthesia for the ambulatory patient. It will be remembered that, in this technique, before each administration the gases are passed into the rebreathing bag from a gun charged with "sparklet" cylinders.

Finally future developments are indicated—surely unanimous approval will be given to the final paragraph of the author's summary to his book which reads as follows:

"Clinics should be set up and made available to all dentists for the treatment of their ambulatory patients lying down on an operating table and under endotracheal anaesthesia administered by an experienced anaesthetist."

Indeed the time has come when properly

equipped centres for dental treatment should be established and dental surgeons led by every inducement possible to think and plan along these lines.

There are six appendices devoted to fainting, case reports, statistics and the questionnaires used during the author's investigations.

This is a thought-provoking and characteristic book and, while some may quarrel at the conclusions reached and the solution proposed, the facts are impressive. The author's purpose will be served if they direct attention even more strongly to this field which has been so neglected.

Cecil Gray

Clinical Applications of Diagnostic and Therapeutic Nerve Blocks. By John J. Bonica, M.D. Published by Blackwell Scientific Publications, Oxford. Pp. 354; illustrated. Price 70*s*.

Dr. Bonica is widely known as the author of the valuable work entitled *The Management of Pain*. This is a very different volume. It is, of course, much shorter and was written, according to the author's preface, to draw the attention of a wider field of clinicians to the scope of nerve blocking procedures. This book is not a manual of techniques, but rather a concise description of the basis for, and the uses of, nerve blocks. Nor is it an over-enthusiastic and uncritical plea for their widespread employment. The author has gone to considerable lengths to present an objective assessment of all the aspects.

The first part, entitled "Basic Considerations", consists of seven chapters. These include a clear and concise discussion dealing with pain processes. It is followed by a section on "The Indications for Nerve Blocks" which to many English readers will seem interestingly broad in its coverage. The "Principles and Requisites for Optimal Results" is in many ways the most valuable chapter in the book and the advice concerning the approach to the patient, the choice of procedure and the appreciation of limitations and disadvantages is excellent. Commenting on techniques, Bonica has again much good advice; not least the too seldom heeded reminder that measures for resuscitation and for the management of complications should always be at hand. The agents available to produce nerve blocks are briefly discussed. A number of these are as yet unavailable in the British Isles. The complications are very well dealt with in a short chapter.

The second part of the volume, entitled "Clinical Considerations", is concerned with the uses of specific block techniques. Many anaesthetists, like the reviewer, will find themselves on unfamiliar territory, in particular when considering pains associated with myofascial syndromes and with bones and joints. The uses of autonomic blocks are fully treated and it is refreshing to note the author's clearly expressed opinions. He does not hesitate, for example, to report the failure of stellate ganglion block in the treatment of several disorders of the head and neck. The innumerable uses of somatic nerve blocks are considered at some length and there are chapters on subarachnoid and extra dural block.

After reading this book one becomes aware that these procedures have much wider possibilities than is generally realized and perhaps should be much more widely employed. Despite Bonica's cautions it is easy to be carried away with enthusiasm, forgetting previous disappointments. Nevertheless this is a good book which is very well worth reading and which should attract many newcomers. The first section in particular commends itself to candidates for the Final F.F.A.R.C.S. examination. The text is adequately illustrated and it is not over-filled with references. There is a well selected bibliography at the back and a satisfactory index. It is well produced and printed and the reviewer noted only one spelling mistake. It is, however, rather expensive.

J. E. Riding

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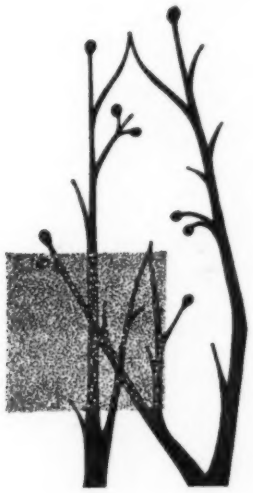

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